ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 210 1971

PARENTAL ATTITUDES IN PEDIATRIC HOSPITAL ADMISSIONS

BY GEORG ROSBERG

ALMQVIST & WIKSELL PERIODICAL COMPANY

PARENTAL ATTITUDES IN PEDIATRIC HOSPITAL ADMISSIONS

By

GEORG ROSBERG

From
Department of Pediatrics,
University of Oulu,
OULU
FINLAND

and from
Children's Hospital,
University of Helsinki,
HELSINKI
FINLAND

Also published as Supplement No. 210 of
Acta Paediatrica Scandinavica 1971

To my Wife and Children

Also published as Supplement No 210 of
Acta Paediatrica Scandinavica 1971

Liikekirjapaino Oy — Helsinki 1971

To my Wife and Children

Introduction

When a child is admitted to hospital the parental psyche is confronted by a situation that is a practical psychological test. The child's admission is attended by many factors which may produce anxiety the strange hospital environment, fear for the child, ignorance of the actual severity of the disease, uncertainty in the face of unfamiliar circumstances, as well as many other subconscious factors

There may be some conflict between physician and parents over the child's therapy the physician may not wish to admit the child because of a shortage of beds or vice versa, the parents may refuse to recognise that the disease, which the physician believes to be serious, requires hospitalization. The parents reaction to a child's admission to hospital reflects only those attitudes and views which are based on their fundamental constitution and psychic structure. It is known that parental refusal is not always related to the stimulus produced by hospital admission All the subconscious factors which may even lead to a violent emotional out burst, in response to a seemingly negligible stimulus must be considered. Without a thorough investigation the physician cannot possibly know the true background of such an outburst. There may be conjugal conflicts, ambivalent situations, general anxiety and stress or strong frustration. There may be a low intelligence level, infantilism, neuroses, psychopathy or even psychoses.

On the other hand, the parents may hide their true feelings and opinions by defence mechanisms and apparently submit to the physician's authority Not all physicians have a keen psychological eye and most of them are so busy that they have no time to speculate on parental behaviour

Straus and coworkers (1961) who analysed the psyche of mothers whose children were frequently admitted to hospital for slight medical indications, usually found the mother-child relationship emotionally good. Rejection attitudes were only noted among mentally retarded mothers of large families.

Waters and Grandall (1964) in their studies on maternal attitudes found that mothers in the lower social classes imposed more restrictions on their children than the mothers of the upper classes. The latter however showed more frequently protective and indulgent attitudes. The authors in addition came to the conclusion that in the last 30 years, the restrictions imposed by mothers on their children had diminished.

Barclay (1965) divided the parents he studied into three groups according to the child's disease, and asked them to formulate their views on concepts like »illness» »hospital» and »physician» along a semantic differential scale. The child's disease or diagnosis definitely affected the parental attitudes.

Cleveland et al. (1965) also chose rheumatoid arthritis as the background against which to study the psychological approach to disease. Rheumatoid arthritis is a prolonged somatic disease, and therefore offers a good basis for studies of the effects of illness on family psychology. The authors found that maternal reactions were correlated with the child's illness. Depression, pessimism, guilt and refusal to admit illness, and other defence reactions were the most common.

Rabkin (1965) pointed out that the clinical communication with parents forms an important factor in parental attitudes. Speaking clearly and understandably to the parents may get their attitudes, expectations and fantasies to interact with the parallel structures representative of the clinic's philosophy.

Strahl (1965) found that parental attitudes to a child's admission to hospital were different in different diagnostic groups. Uncertainty in the case of hospitalization is particularly noticeable in admissions for a psychogenic disorder. The author also described several reasons which led parents to seek admission for their child, such as the parents' psychic or physical fatigue in caring for a disturbed child, or uncertainty in the parental role. The background factors here included maternal feelings of guilt, jealousy or lack of confidence in the nurses, or general anxiety. Strahl also devoted attention to the physician's role when he encounters the parents of a psychically disturbed child, to the seeds of conflict present in this situation, and to the chances of therapy.

Stone and Rowley (1965) found out in their study about the relationship between the professed attitudes of parents of »problem» children and the type of problem manifested by the child that there was significant difference between mothers of personality problem children and mothers of conduct-problem children. The former mothers were more excessive in their demands for striving.

Malmquist (1965) noted that it was harder to get lower class families to participate in treatment in child psychiatric clinics. Lower class families demanded immediate symptomatic relief and lacked understanding of the »basic» problem.

Szyrynski (1965) pointed out that working with the parents is particularly important in respect to the younger children. It is only in adolescence that the therapist may attempt to help his young patients in gaining insight into their psychological relationship with the parents. In child-psychiatry the parents may also expect the child to be »fixed» by a psychiatrist and returned in an improved condition.

Marcellus and Hawke (1966) studied the attitude of the parents of severely paralysed children and found that the majority wished to keep their children at home. The diagnosis when made, had been a dreadful shock, and the parents refused to believe in the poor prognosis. Only some of them were capable of a realistic assessment of the situation. In addition, they believed that it was better for the child's emotional development to stay at home.

Review of the literature

Prugh's (1953) extensive study concentrated on the effect of hospitalization on children but also included parental reactions. He pointed out that, in addition to the parents realistic fear of disease, there may be feelings of guilt and anxiety and defence mechanisms with their projection on the clinic personnel. The parents may consider the child's disease as some kind of punishment, the mother may be jealous of the nurses, or worried about the child's regression as a result of hospitalization Prugh also pointed out that the mother may have sadistic impulses toward the child In some cases the parents psychologic reactions were so pronounced that psychotherapy was required to help them to adopt a realistic attitude to the child's hospitalization and illness. Feelings of guilt and anxiety sometimes prevented parental visits to the child. In these cases the child parent relationship was often otherwise unsatisfactory

Blom and Nicholls (1954) studied the reactions of the parents of rheumatic children while searching for the psychological disorders of these children. They concluded »Because the mothers mistrusted themselves so deeply they reacted very strongly to anything which seemed to corroborate their inadequacy.» The authors also emphasized that it was more difficult to obtain information on paternal attitudes since the father's relationship to the child was overshadowed by the more intense relationship of the mother Inclusion of the mothers in psychotherapy for the children (casework with mothers) considerably changed the mothers attitude to hospital and hospital personnel

Schonell (1956) devoted attention to the influence a mentally defective child has on the family A mentally retarded child in particular colours the behaviour of its mother In the presence of outsiders the mother of such a child is seized by anxiety The mother feels that her child is a heavy burden and would be grateful if someone else made her life temporarily easier by caring for the child (This may be a contributory factor when the mother seeks hospital admission for the child) Schonell also found that in many cases an underdeveloped child affected the whole family's normal habits such as eating and sleeping A mentally defective child also irritated or depressed all the family members.

Hollingshead and Redlich (1958, p. 336), discussing the attitude towards psychiatry found that in the higher social classes it was more favourable than in the lower classes.

Lidz et al (1958) in their study of the psychodynamics of a family used quantities measuring small-group dynamics. Parental personality was studied, and the reflecting factors were internal family relations to a psychically ill and a psychically healthy child. The results showed that the attitudes of the parents were based on their own social and religious background and their subconscious and conscious attitudes to conjugal and parental roles

Crecraft (1959) noted that children cannot benefit from treatment until »permitted» to do so by their parents. The response of children to the treatment is in part determined by the parents attitude towards the therapy

Straus and coworkers (1961) who analysed the psyche of mothers whose children were frequently admitted to hospital for slight medical indications, usually found the mother-child relationship emotionally good Rejection attitudes were only noted among mentally retarded mothers of large families.

Waters and Grandall (1964) in their studies on maternal attitudes found that mothers in the lower social classes imposed more restrictions on their children than the mothers of the upper classes The latter however showed more frequently protective and indulgent attitudes. The authors, in addition, came to the conclusion that in the last 30 years the restrictions imposed by mothers on their children had diminished.

Barclay (1965) divided the parents he studied into three groups according to the child s disease, and asked them to formulate their views on concepts like »illness» »hospital» and »physician» along a semantic differential scale. The child s disease or diagnosis definitely affected the parental attitudes.

Cleveland et al. (1965) also chose rheumatoid arthritis as the background against which to study the psychological approach to disease. Rheumatoid arthritis is a prolonged, somatic disease, and therefore offers a good basis for studies of the effects of illness on family psychology The authors found that maternal reactions were correlated with the child's illness. Depression pessimism, guilt and refusal to admit illness, and other defence reactions were the most common.

Rablin (1965) pointed out that the clinical communication with parents forms an important factor in parental attitudes Speaking clearly and understandably to the parents may get their attitudes, expectations and fantasies to interact with the parallel structures representative of the clinic s philosophy

Strahl (1965) found that parental attitudes to a child s admission to hospital were different in different diagnostic groups Uncertainty in the case of hospitalization is particularly noticeable in admissions for a psychogenic disorder The author also described several reasons which led parents to seek admission for their child, such as the parents psychic or physical fatigue in caring for a disturbed child or uncertainty in the parental role. The background factors here included maternal feelings of guilt, jealousy or lack of confidence in the nurses, or general anxiety Strahl also devoted attention to the physician s role when he encounters the parents of a psychically disturbed child to the seeds of conflict present in this situation and to the chances of therapy

Stone and Rowley (1965) found out in their study about the relationship between the professed attitudes of parents of »problem» children and the type of problem manifested by the child that there was significant difference between mothers of personality-problem children and mothers of conduct problem children The former mothers were more excessive in their demands for striving

Malmquist (1965) noted that it was harder to get lower class families to participate in treatment in child psychiatric clinics Lower class families demanded immediate symptomatic relief and lacked understanding of the »basic» problem.

Szyrynski (1965) pointed out that working with the parents is particularly important in respect to the younger children. It is only in adolescence that the therapist may attempt to help his young patients in gaining insight into their psychological relationship with the parents In child-psychiatry the parents may also expect the child to be »fixed» by a psychiatrist and returned in an improved condition

Marcellus and Hawke (1966) studied the attitude of the parents of severely paralysed children and found that the majority wished to keep their children at home. The diagnosis when made, had been a dreadful shock, and the parents refused to believe in the poor prognosis. Only some of them were capable of a realistic assessment of the situation. In addition, they believed that it was better for the child's emotional development to stay at home.

Kahn and coworkers (1966) found that the *institution serving upper class patients* had the highest proportion of patients treated in traditional psychotherapy and the lowest average of improvement, while the institution serving lower class patients had a higher proportion of somatic therapy treatments and better rates of improvement. The authors suggested that differences in treatment were more related to staff attitudes and social class than to psychiatric *differences in the populations*

Davidson and Schrag (1969) pointed out that the attitudes of the parents proved to be one of the most significant factors in determining whether the recommendations of the psychiatrist were carried out or not. If the parents' view of the problem agreed with that of the psychiatrist, they were far more apt to accept the psychiatric recommendation than *if they disagreed or saw a related* problem The authors underline how important it is for child psychiatrists to identify the parents attitude toward their child s problem and to try to change the *attitude if it is incorrect.*

McDermott and coworkers (1970) compared the evaluation and treatment of lower lower middle and upper middle class children. They could not find any significant differences among the three groups at the termination of treatment, but longer duration of treatment was associated with greater improvement in the upper middle class than in the two *other classes* The authors point out that class related differences may depend on the difficulties in application of traditional therapeutic modes to lower class patients

The parental attitude toward child psychiatric hospital treatment was favourable in 80 per cent in a Finnish study of 1969 (Rosberg 1970) Hospital treatment encountered the same degree of opposition among all social classes The parents had postponed *bringing their child to hospital* more often in lower social classes An over protective attitude towards the child was more common in the highest social group

Purpose of the study

The purpose of this study was

I *to analyse parental attitudes towards* hospital and hospital personnel in Finnish pediatric hospitals with special reference to mental disorders and functional symptoms

II to correlate different maternal and paternal attitudes with social and psychological indications for hospital admission of children.

III *to discover the effect of certain social* background factors on the parental attitudes

IV to analyse maternal attitudes in different diagnostic groups of children s diseases.

Material and methods

An extensive investigation was carried out in Finland in 1963—64 into indications for child admission to hospital. During three separate investigation periods, together 4 months covering a 12 months period a special questionnaire, with 70 medical, socioeconomical and family psychological questions, was completed for each admission into twentyone pediatric departments. The total number of beds for children in the participating hospitals was 1462 and the total number of children treated in them in 1963 was 28 635. The investigation material thus covered 27,8 per cent of all children admitted to hospital in Finland during the whole year. The investigation has been described in detail in supplement 196 in Acta Paediatrica Scandinavica (Rosberg 1969) *

In the present study the questions dealing with parents attitudes in the material mentioned above are studied closer. The last two sides of the questionnaire are shown in Appendix.

The questions dealing with parents attitudes (Nos. 40—44) were filled in by ward nurses when the child was discharged from the hospital. The nurses had had several opportunities to make observations on parental attitudes e.g. during visiting hours.

The last six items dealing with diagnosis and some hospital factors were completed by the physician in charge of the ward when the patient was discharged. The physician made his judgement for each case as a whole taking into consideration the whole hospitalization period.

In the classification of diagnosis the four-digit figures of the international nomenclature of diseases were used (WHO 1948). The numbers for the diagnosis groups are presented below and are compared with the last WHO nomenclature (1968).

	WHO 1948	WHO 1968
Mental disorders	300—326	290—315
Functional symptoms	780—785 and 790—795	780—784 and 790—793
Congenital malformations	750—759	740—759
Neonatal diseases	760—776	760—779
Accidents	800—999	800—999

The group of so-called »functional symptoms» was selected to represent psychosomatic symptoms in the cases parents had brought their child to hospital without the general practitioner being able to make any specific diagnosis.

The whole material consisted of 7954 pediatric patients. The group of children's psychiatric diseases comprised 265 patients, the group of functional symptoms 588 patients, congenital malformations 595 children, neonatal diseases 623 and 473 children were admitted to hospital for accidents.

The questionnaire items »unusually inclined to spoil the child» and »unusually protective» were combined under the

) The investigation was financially supported by the Ane and Signe Gyllenberg Foundation.
) This investigation was financially supported by th Foundation for Medical Resea ch in Finland (Suomen Lääketieteen Säätiö)

heading »over protective» Similarly »rejectives» and »indifferent» attitudes were combined as »negative attitude» The difference between clearly rejecting and negatively indifferent can be impossible to define in practice.

For social background factors, only two were selected aggregate parental income and number of children in the family 600 Fmk was at that time equivalent to 186 U S $ and 1000 Fmk to 310 U S $

Statistical techniques

Statistical techniques The control group consisted of »other diseases» in tables analysing different attitudes in different diagnostic groups. In the other tables the normal ttitudes group served as the control group against which other groups of attitudes were compared. The t-test was used in significance calculations. The Elliot 803 of the Oulu University Computer Centre carried out the calculations.

Three levels of significance were used:

- highly significant ($p \leq 0.001$)
- significant ($0.001 < p \leq 0.01$)
- almost significant ($0.01 < p \leq 0.05$)

Results

TABLE 1

PARENTAL ATTITUDES TOWARDS HOSPITAL AND HOSPITAL PERSONNEL

	Mental disorders	Functional symptoms	Other diseases	Total
Favourable	221 (83.4 %)***	527 (89.6 ,,)	6500 (91.6 %)	7248 (91.2 %)
Indifferent	9 (3.4 %)*	3 (0.5 %)**	85 (1.2 %)	97 (1.2 %)
Negative	9 (3.4 %)	11 (1.9 %)	77 (1.1 %)	97 (1.2 ,,)
Indefinable	22 (8.3 %)	41 (7.0 %)	409 (5.8 %)	472 (6.0 %)
The child came from an institution	4 (1.5 %)	6 (1.0 %)	25 (0.3 %)	35 (0.4 %)
Total	265 (100 %)	588 (100 %)	7096 (100 %)	7949 (100)
			Not reported	5
				7954

In the mental disorders group a favourable attitude was less frequent than in the other diseases group. The difference was highly significant. Negative or indefinable attitudes were more frequent in the mental than in the control group of other diseases. The differences were significant. In the functional symptoms group the negative or indefinable attitudes were less frequent than in the other diseases group. The difference was significant.

TABLE 2.

MATERNAL ATTITUDE TOWARDS THE CHILD ACCORDING TO THE INDICATION FOR HOSPITAL ADMISSI

	Over protective	Negative or indefinable	Normal	Total
Purely medical indications	437 (83.3 %)**	777 (86.5 %) **	5677 (91.9 %)	6891 (90.7 %)
Partly also social indications	40 (7.6 %)	91 (10.1 %)	399 (6.5 %)	530 (6.9 %)
Psychological factors in the family	48 (9.1 %)	30 (3.4 %)***	101 (1.6 %)	179 (2.4 %)
Total	525 (100.0 %)	898 (100.0 %)	6177 (100.0 %)	7600 (100.0 %)
			Not reported	354
				7954

When the child was admitted for purely medical indications, the mother's attitude towards him was over protective less frequently than normal. The difference was highly significant. Over protective attitudes were more frequent when admission had also been influenced by psychological factors in the family. The difference was highly significant.

When the maternal attitudes were indefinable or negative, admissions for purely medical indications were fewer than in the group where the attitude was normal. The difference was highly significant. When social or psychological indications had affected the admission the maternal attitude was negative or indefinable more frequently than in the control group of other diseases, where the attitude was classified as normal. The differences were highly significant.

TABLE 3.

PATERNAL ATTITUDE TOWARDS THE CHILD ACCORDING TO THE INDICATION FOR HOSPITAL [illegible]

	Over protective	Negative or indefinable	Normal	Total
Purely medical indications	217 (86.8 %)**	2021 (85.6 %)	4653 (93.3 %)	6891 (90.7 %)
Partly also social indications	9 (3.6 %)	272 (11.5 %)	249 (5.0 %)	530 (6.9 %)
Psychological factors in the family	24 (9.6 %)	68 (2.9 %)	87 (1.7 %)	179 (2.4 %)
Total	250 (100.0 %)	2361 (100.0 %)	4989 (100.0 %)	7600 (100.0 %)
			Not reported	354
				7954

When the child was admitted for purely medical indications the paternal attitude to the child was found to be over protective less frequently than normal. The difference was highly significant. When psychological factors inside the family affected the admission of the child, the paternal attitude was over-protective more frequently than normal. The difference was highly significant.

When the paternal attitude was negative or indefinable all groups of indications were found to differ highly significantly from the groups of normal behaviour. Admissions for purely medical indications were fewer, while admissions for social and psychological indications were more frequent.

TABLE 4

MATERNAL ATTITUDE TO THE CHILD ACCORDING TO THE AGGREGATE PARENTAL INCOME

	Over protective	Negative or indefinable	Normal	Total
≤ 600 Fmk/mo.	199 (40.2 %)	341 (44.9 %)**	2278 (39.6 %)	2218 (40.[illegible] %)
≤ 1000 Fmk/mo.	144 (29.1 %)	172 (22.6 %) **	1820 (31.6 %)	2136 (30.5 %)
> 1000 Fmk/mo.	113 (22.8 %)**	64 (8.4 %)	914 (15.9 %)	1091 (15.6 %)
Farmer family	39 (7.9 %)	183 (24.1 %)**	744 (12.9 %)	966 (13.7 %)
Total	495 (100.0 %)	760 (100.0 %)	5756 (100.0 %)	7011 (100.0 %)
			Not reported	943
				7954

Results

TABLE 1

PARENTAL ATTITUDES TOWARDS HOSPITAL AND HOSPITAL PERSONNEL

	Mental disorders	Functional symptoms	Other diseases	Total
Favourable	221 (83.4 %)	527 (89.6 %)	6500 (91.6 %)	7248 (91.2 %)
Indifferent	9 (3.4 %)**	3 (0.5 %)	85 (1.2 %)	97 (1.2 %)
Negative	9 (3.4 %)	11 (1.9 %)	77 (1.1 %)	97 (1.2 %)
Indefinable	22 (8.3 %)	41 (7.0 %)	409 (5.8 %)	472 (6.0 %)
The child came from an institution	4 (1.5 %)	6 (1.0 %)	25 (0.3 %)	35 (0.4 %)
Total	265 (100 %)	588 (100 %)	7096 (100 %)	7949 (100 %)
			Not reported	5
				7954

In the mental disorders group a favourable attitude was less frequent than in the other diseases group. The difference was highly significant. Negative or indefinable attitudes were more frequent in the mental than in the control group of other diseases. The differences were significant. In the functional symptoms group the negative or indefinable attitudes were less frequent than in the other diseases group. The difference was significant.

TABLE 2.

MATERNAL ATTITUDE TOWARDS THE CHILD ACCORDING TO THE INDICATION FOR HOSPITAL ADMISSION

	Over protective	Negative or indefinable	Normal	Total
Purely medical indications	437 (83.3 %) **	777 (86.5 %)	5677 (91.9 %)	6891 (90.7 %)
Partly also social indications	40 (7.6 %)	91 (10.1 %)	399 (6.5 %)	530 (6.9 %)
Psychological factors in the family	48 (9.1 %)***	30 (3.4 %)***	101 (1.6 %)	179 (2.4 %)
Total	525 (100.0)	898 (100.0 %)	6177 (100.0 %)	7600 (100.0 %)
			Not reported	354
				7954

When an only child was admitted hospital the mother's attitude toward tl child was more often over protective tl normal. When the family had 4 children the attitude of the mothe

tl over protective than nor he family had more than 3 tl mother's attitude became n definable towards the sick

TERNAL ATTITUDE TO THE CHIL ... F CHILDREN IN THE AMILY

	Over protecti		Normal	Total
One child	98 (39 3		1330 (26 8 %)	2060 (27 4 %)
2 — 3 children	113 (45 4		7666 (53.7 %)	3948 (52.6 %)
4 — 5 children	34 (13.7		711 (14.3 %)	1110 (14.8 %)
6 — 12 children	4 (1.6		25[illegible] (5.2 %)	390 (5.2 %)
Total	249 (100 0	1 #	4963 (100 0 %)	7508 (100.0 %)
			Not reported	446
				7954

The father seemed to be over protective more often than normal when an only child was hospitalized When the family had 2—3 children or more than 6 children the attitude of the father was less fre quently over protective than normal.

The paternal attitude was negative or indefinable when the family had 2—5 children.

TABLE 8

MATERNAL ATTITUDE TO THE D WITH M DISORDERS OR FUNCTIONAL SYMPTOMS

	Mental disorders	Functional symptoms	Other diseases	Total
Normal	152 (57.3 %) **	448 (76.2 %) **	5815 (82.0 %)	6415 (80.7 %)
Over-protective	45 (17 0 %)	51 (8 7 %)	451 (6.4 %)	547 (6.9 %)
Negative	64 (24.2)***	83 (14 1 %)*	810 (11.3 %)	948 (12.0 %)
The child came from an institution	4 (1 5)	6 (1 0 %)	23 (0.4 %)	25 (0.4 %)
Total	265 (100.0)	588 (100 0 %)	7092 (100.0 %)	7945 (100.0 %)
			Not reported	9
				7954

In the mental disorders group a normal attitude was found to be less frequent than in the other diseases. The difference was highly significant Over protective, negative and indefinable attitudes were more frequent in the mental disorders group than in the group of other diseases. The differences were highly significant.

In the functional symptoms group normal attitudes were also found to be less frequent than in the »other diseases» group The difference was highly significant. Over protective or negative or indefinable attitudes were more frequent in the functional symptoms group than in the »other diseases» group. The differ ences were almost significant

TABLE 9

MATERNAL ATTITUDE TO THE CHILD WITH CONGENITAL MALFORMATION OR NEONATAL DISEASE

	Congenital malformations	Neonatal diseases	Other diseases	Total
Normal	483 (81.2 %)	454 (72.9 %)	5478 (81 4 %)	6415 (80.7 %)
Over protective	33 (5.5 %)	13 (2.1 %)	501 (7.5 %)	501 (6.9 %)
Negative or indefinable	79 (13.3 %)	153 (34 6 %)	716 (10.6 %)	948 (12.0 %)
The child came from an institution	0 (0.0 %)	3 (0.4 %)	32 (0.5 %)	35 (0.4 %)
Total	595 (100.0 %)	623 (100.0 %)	6727 (100.0 %)	7945 (100.0 %)
			Not reported	9
				7954

In congenital malformations the maternal attitude was over protective less frequently than in the »other diseases» group The difference was significant. Negative or indefinable attitudes were more frequent than in the control group of other diseases The difference was almost significant. The series contained no institutionalized children with congenital malformations.

The maternal attitudes to children with neonatal diseases were over protective less frequently than in the »other diseases» group The attitude was very frequently rejecting, indifferent or indefinable. The difference between neonatal diseases and other diseases was highly significant.

TABLE 10.

MATERNAL ATTITUDE TO THE CHILD HOSPITALIZED FOR AN ACCIDENT

	Accidents	Other diseases	Total
Normal	414 (87.5 %)**	6001 (80.3 %)	6415 (80.7 %)
Over protective	19 (4.0 %)**	528 (7.0 %)	547 (6.9 %)
Negative or indefinable	40 (8.5 %)	908 (12.2 %)	948 (12.0 %)
The child came from an institution	0 (0.0 %)	35 (0.5 %)	35 (0.4 %)
Total	473 (100.0 %)	7472 (100.0 %)	7945 (100.0 %)
		Not reported	9
			7954

The maternal attitude to a child admitted to hospital for an accident was normal more frequently than in the control group of other diseases The difference was highly significant. Over protective, negative or indefinable attitudes towards a child hospitalized for an accident were less frequent than in the control group

Discussion

The material was collected in many pediatric hospitals all over Finland. The patients were common pediatric cases without any selection. It is seen that the parental attitudes in the pediatric hospitals were in general favourable (91.2 %).

Mental disorders seemed to be the group most clearly arousing various dissenting attitudes in the parents. In their relationship to the hospital and staff, too the same finding emerges. Some of this must probably be attributed to the fact that the staff of children's psychiatric wards is more used to psychic aspects and is thus better trained to observe parental behaviour than are the personnel of e.g. the surgical wards. But it must be pointed out that the parents are reluctant to accept a psychic diagnosis, since they realize that the cause will be sought for or is, in themselves. The result can be hostility towards the physician or hospital.

One explanation may be that the parents of psychically sick children are relatively often themselves mentally disturbed, and that the child's mental disorder exposes the parents to considerable stress, which often leads them to seek release in hostility towards the staff. It should always be borne in mind that some of the parents of children suffering from mental disorders have themselves been treated in psychiatric institutions.

In the indications for hospital admission there was a clear correlation between over protectiveness and »psychological factors in the family». Naturally an over protective mother while urging the admitting physician to take her child to hospital can be »a psychological factor» and this factor is seen also during hospital treatment. We can say that it was possible for an over-protective mother to get her child into hospital with minor medical indications. The same was true of paternal attitudes towards the sick child.

The association of social factors with a negative attitude agrees with the earlier finding that in the lower social classes the attitudes of parents to their children are, on the whole, shorter lived, more aggressive and more negative. This also applies when the child is admitted for social reasons: the behaviour of the parents may show a negative attitude towards the child. Difficult social conditions may also make it impossible for the parents to visit the child often enough, and the attitude remains undefined.

In the different income groups there was more over protectiveness in the highest income group both in mothers and fathers and more often negative attitudes in the lowest income group. The reason for negative or indefinable attitudes in farmer fathers may be that they are so busy on their farms and so rarely visit the hospital that their attitude remains »indefinable».

When the number of children increased the over-protectiveness decreased, which is understandable. An only child gets more attention and more »spoiling» than do members of a big family.

In the different diagnostic groups there were distinct lines of maternal attitudes: more frequent over protectiveness in mental disorders and functional symptoms. The same was true of negative

TABLE 9

MATERNAL ATTITUDE TO THE CHILD WITH CONGENITAL MALFORMATION OR NEONATAL DISEASE

	Congenital malformations	Neonatal diseases	Other diseases	Total
Normal	483 (81.2 %)	454 (72.9 %)	5478 (81.4 %)	6415 (80.7 %)
Over-protective	33 (5.5)	13 (2.1 %)*	501 (7.5 %)	501 (6.9 %)
Negative or indefinable	79 (13.3 %)	153 (34.6)	716 (10.6 %)	948 (1[illegible]0 %)
The child came from an institution	0 (0.0 %)	3 (0.4 %)	32 (0.5 %)	35 (0.4)
Total	595 (100.0 %)	623 (100.0 %)	6727 (100.0 %)	7945 (100.0 %)
			Not reported	9
				7954

In congenital malformations the maternal attitude was over protective less frequently than in the »other diseases» group. The difference was significant. Negative or indefinable attitudes were more frequent than in the control group of other diseases. The difference was almost significant. The series contained no institutionalized children with congenital malformations.

The maternal attitudes to children with neonatal diseases were over protective less frequently than in the »other diseases» group. The attitude was very frequently rejecting, indifferent or indefinable. The difference between neonatal diseases and other diseases was *highly significant*.

TABLE 10.

MATERNAL ATTITUDE TO THE CHILD HOSPITALIZED FOR AN ACCIDENT

	Accidents	Other diseases	Total
Normal	414 (87.5)	6001 (80.3)	6415 (80.7)
Over-protective	19 (4.0 %)***	528 (7.0)	547 (6.9 %)
Negative or indefinable	40 (8.5 %)***	908 (12.2)	948 (12.0 %)
The child came from an institution	0 (0.0)***	35 (0.5 %)	35 (0.4)
Total	473 (100.0 %)	7472 (100.0 %)	7945 (100.0)
		Not reported	9
			7954

The maternal attitude to a child admitted to hospital for an accident was normal more frequently than in the control group of other diseases. The difference was highly significant. Over protective, negative or indefinable attitudes towards a child hospitalized for an accident were less frequent than in the control group.

Discussion

The material was collected in many pediatric hospitals all over Finland. The patients were common pediatric cases without any selection. It is seen that the parental attitudes in the pediatric hospitals were in general favourable (91.2 %).

Mental disorders seemed to be the group most clearly arousing various dissenting attitudes in the parents. In their relationship to the hospital and staff, too the same finding emerges. Some of this must probably be attributed to the fact that the staff of children's psychiatric wards is more used to psychic aspects and is thus better trained to observe parental behaviour than are the personnel of e.g. the surgical wards. But it must be pointed out that the parents are reluctant to accept a psychic diagnosis since they realize that the cause will be sought for or is, in themselves. The result can be hostility towards the physician or hospital.

One explanation may be that the parents of psychically sick children are relatively often themselves mentally disturbed, and that the child's mental disorder exposes the parents to considerable stress, which often leads them to seek release in hostility towards the staff. It should always be borne in mind that some of the parents of children suffering from mental disorders have themselves been treated in psychiatric institutions.

In the indications for hospital admission there was a clear correlation between over-protectiveness and »psychological factors in the family». Naturally an over protective mother while urging the admitting physician to take her child to hospital can be »a psychological factor» and this factor is seen also during hospital treatment. We can say that it was possible for an over-protective mother to get her child into hospital with minor medical indications. The same was true of paternal attitudes towards the sick child.

The association of social factors with a negative attitude agrees with the earlier finding that, in the lower social classes the attitudes of parents to their children are, on the whole, shorter-lived, more aggressive and more negative. This also applies when the child is admitted for social reasons: the behaviour of the parents may show a negative attitude towards the child. Difficult social conditions may also make it impossible for the parents to visit the child often enough, and the attitude remains undefined.

In the different income groups there was more over protectiveness in the highest income group both in mothers and fathers and more often negative attitudes in the lowest income group. The reason for negative or indefinable attitudes in farmer fathers may be that they are so busy on their farms and so rarely visit the hospital that their attitude remains »indefinable».

When the number of children increased the over-protectiveness decreased, which is understandable. An only child gets more attention and more »spoiling» than do members of a big family.

In the different diagnostic groups there were distinct lines of maternal attitudes: more frequent over-protectiveness in mental disorders and functional symptoms. The same was true of negative

attitudes, and thus shows that the maternal psyche can react both positively and negatively to the child's disease. In accidents over protective attitudes in mothers were less frequent. An over protective mother may be more on her guard against accidents so that fewer are incurred by her children.

The negative attitudes in the diagnostic groups of congenital malformations and neonatal diseases may depend on different factors. In a case of congenital malformation there can be true rejection of the child but in neonatal disease the mother also stays in the hospital and her attitude can therefore not be defined

Summary

Data on 7954 pediatric hospital patients were collected in Finland and in the present study the parental attitudes in these cases were analysed.

In the mental disorders group a favourable parental attitude towards hospital and hospital personnel was less frequent and a negative attitude more frequent than in the other diseases.

In the group of so-called functional symptoms — considered as psychosomatic diseases — the negative or indefinable attitude towards hospital and hospital personnel was less frequent than in the control group of other diseases.

When the maternal and paternal attitudes were studied according to the indication for hospital admission it was found that when psychological factors had influenced the admission, the attitude was over-protective more often than normal. When the factors were both psychological and social, the attitude was negative or indefinable more frequently than normal. The over protectiveness correlated with psychological factors and the negative or indefinable behaviour with both social and psychological factors in hospital admission.

Two social factors were selected for correlation with different attitudes: the aggregate parental income and the number of children in the family. The correlation showed that over protectiveness was more frequent in the highest income bracket and when an only child was admitted to hospital. The negative or indefinable maternal or paternal attitudes were more frequent in the lowest income bracket and in farming families. Also when there were more than 3 children in the family the maternal attitude became negative or indefinable.

The maternal attitude was also analysed in different diagnostic groups. Groups such as mental diseases and children's accidents were selected because they were clearly as dissimilar as possible. All groups were compared with the group of »other diseases».

The maternal attitude towards a child suffering from mental disorders or functional symptoms was more frequently over protective or negative or indefinable than in the group of other diseases.

The maternal attitude towards a child suffering from congenital malformation was less frequently over protective than when the child had some other disease. The same was true of children with neonatal diseases. In the group of neonatal diseases the maternal attitude was also more often negative or indefinable than in the other diseases.

In children's accidents the maternal attitude was less frequently over protective or negative or indefinable than in the other diseases.

References

1 Armstrong, R. M. Approaches to family involvements in delinquency *World Medical Journal* 14 49 1967

2 Barclay A. Parental attitudes toward children's hospitalization experiences. *Psychol Reports* 17 761 1965

3 Blom, G E. and Nicholls, G Emotional factors in children with rheumatoid arthritis. *Amer J Orthopsychiat* 24 588, 1954

4 Cleveland S E., Reitman E. E and Brewer, E. J Psychological factors in juvenile rheumatoid arthritis. *Arthr and Rheum* 8 1152 1965

5 Crecraft H Treatment in a child guidance clinic. *Dis Nerv Syst* 20 518 1959

6. Davidson P O., and Schrag A. R. Factors affecting the outcome of child psychiatric consultations. *Amer J Orthopsychiat* 39 774 1969

7 Hallman, N and Wasz Höckert O Indications for hospitalization of children in Finland. *Mod Probl Pädiat* IX 11 1965

8. Hollingshead A. and Redlich, F C. *Social class and mental illness a community study* John Wiley & Sons, Inc. New York 1958

9 Kahn R. L., Fink, M. and Siegel, N Sociopsychological aspects of psychiatric treatment. *Arch Gen Psychiat.* 14 20, 1966

10. Lidz, T., Fleck, S., Cornelison, A and Terry D The intrafamilial environment of the schizophrenic patient IV Parental personalities and family interaction. *Amer J Orthopsychiat* 28 764 1958

11 Malmquist C. P Psychiatric perspectives on the socially disadvantaged child. *Compr Psychiat* 6 176 1965

12. Marcellus, D and Hawke, W A. Survey of attitudes of parents of children with cerebral palsy in Windsor and Essex County Ontario *Canad Med Ass J* 95 1242, 1966

13 McDermott J F., Harrison, S I., Schrager, J., Killins, E. W and Dickerson B. Social class and child psychiatric practice The clinician's evaluation of the outcome of therapy *Amer J Psychiat* 126 7 1970

14 Prugh, D G., Staub, E. M., Sands, H Kirschbaum, R. M and Lenihan E. A. A study of the emotional reactions of children and families to hospitalization and illness. *Amer J Orthopsychiat* 23 70, 1953

15 Rabkin L. Y Sources of strain in the treatment of disturbed children and their families. *Mental Hyg* 49 544 1965

16. Rosberg, G Social and psychological factors in hospital admission of children with special reference to mental disorders and functional symptoms. *Acta Paediat Scand* Suppl 196, 1969

17 Rosberg G Vanhempien asenteet ja lastenpsykiatrinen sairaalahoito (Parental attitudes in child psychiatric hospital admission) *Sosiaalilääk Aikak* 8 67 1970

18 Schonell, F J and Watts, B. H A first study of the effects of a subnormal child on the family unit. *Amer J Ment Defic* 61 210 1956

19 STONE, B F and ROWLEY V N Children's behaviour problems and parental attitudes. *J Gen Psych* 107 281 1965

20 STRAHL, M Über die Einstellung der Eltern zur Krankenhausaufnahme ihres Kindes. *Med Klin* 60 1422 1965

21 STRAUS, P., COIFFARD N., MARZO-WEYL, S and LENOIR M *L hospitalization des enfants Une étude de pediatrie sociale dans l'agglomération parisienne* Monographie de L Institut National d'Hygiene No 23 Paris 1961

22 SZYRYNSKI, V Psychotherapy with parents of maladjusted children *Canad Psych Ass J* 10 350 1965

23 WATERS, E. and GRANDALL, V J Social class and observed maternal behaviour from 1940 to 1960 *Child Develop* 35 1021 1964

Georg Rosberg, M. D

Address

Keskusmielisairaala
OULU
Finland

Appendix

TO BE COMPLETED BY WARD SISTER ON THE CHILD'S DISCHARGE
(or at the latest, on the day the form is due to be returned)

	27	28	29

40. IF THE CHILD HAS BEEN DISCHARGED HOW LONG DID HE STAY

__________ DAYS

IF HE HAS NOT BEEN DISCHARGED, HE REMAINED IN THE HOSPITAL ON (DATE) ____/_____ 196__

30

41. HOW LONG DID THE CHILD HAVE TO WAIT FOR ADMISSION

__________ DAYS/WEEKS/MONTHS

31

42. WAS THE PARENTS'/FOSTER PARENTS' ATTITUDE TO HOSPITAL AND HOSPITAL PERSONNEL

- [1] FAVOURABLE
- [ ] INDIFFERENT
- [ ] NEGATIVE
- [6] IMPOSSIBLE TO SAY
- [7] THE CHILD CAME FROM AN INSTITUTION

	32	33

43. WAS THE PARENTS'/FOSTER PARENTS' ATTITUDE TO THE CHILD

FATHER	MOTHER	
[1]	[ ]	UNUSUALLY PROTECTIVE
[ ]	[ ]	UNUSUALLY SPOILING
[3]	[3]	NORMAL
[ ]	[ ]	SLIGHTING OR INDIFFERENT
[8]	[8]	IMPOSSIBLE TO SAY
[10]		THE CHILD CAME FROM AN INSTITUTION

34

44. ON DISCHARGE THE CHILD WAS

- [1] CONVALESCENT
- [2] UNIMPROVED
- [ ] UNTREATED
- [ ] DEAD
- [ ] REMAINED IN HOSPITAL AFTER THE FORM WAS RETURNED

DATE ___/ 196_

WARD SISTER'S SIGNATURE

TO BE COMPLETED BY PHYSICIAN ON THE CHILD'S DISCHARGE
(or at the latest, on the day the form is due to be returned)

1. DIAGNOSIS AT OUTPATIENT CLINIC ON ADMISSION	35	36
DIAGNOSIS ON DISCHARGE (IF DISCHARGED)	37	38

3. DO YOU FIND THAT THE CHILD WAS ADMITTED (CROSS) — 39

- [1] ON PURELY MEDICAL INDICATIONS
- [2] PARTLY ALSO FOR SOCIAL REASONS
- [3] DECISIVELY FOR SOCIAL REASONS
- [ ] PARTLY OR DECISIVELY DUE TO PSYCHOLOGICAL FACTORS IN THE FAMIL

4. DO YOU FIND THAT THE PARENTS — 40

- [1] CONSULTED THE PHYSICIAN THE HOSPITAL IN TIME
- [2] CONSULTED THE PHYSICIAN THE HOSPITAL TOO LATE

5. DO YOU FIND THAT THE CHILD HAD APPARENTL BEEN NEGLECTED T HOME — 41

- [ ] YES
- [2] NO

COULD THE CHILD HAVE BEEN DISCHARGED EARLIER? — 42
(TO BE COMPLETED ONL THE CHILD HAS BEEN DISCHARGED)

- [ ] YES, IF THE CHILD'S HOME CONDITIONS HAD BEEN BETTER
- [ ] YES, IF THE CHILD S HOME HAD BEEN BETTER LOCATED
- [ ] YES, HAD THE CHILD NOT ACQUIRED AN INFECTION IN HOSPITAL
- [4] YES, IF THERE HAD BEEN NO WAITING PERIOD BEFORE EXAMINATIONS
- [6–9] YES, IF THE FOLLOWING CONDITIONS HAD BEEN MET

- [5] NO

DATE TN_

PHYSICIAN'S SIGNATURE

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics. Lisbon, 1962.* Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic study. Sw. kr. 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr. 25.— 1964
157. Brante, G., Kaijser, K. and Ockerman, P. A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Pediatric Congress, Stockholm, 1964.* Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Ockerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Peltonen, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
Glasser, L. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., ...tosis: A Review of 187 Cases in Children with Follow-...y Function Studies in 51. Sw. kr. 20.— 1966
...Anne-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 15.— 1966
...Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children, a Longitudinal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 20.— 1966
172. *Festschrift in Memory of* [illegible]. Sw. kr. 15.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hinkkanen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress, Bergen, 1967.* Sw. kr. 35.— 1967
178. Sjögren, Inbe, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodologic... and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Huma... Placental Lipid Metabolism and Transport. Sw. kr. 25.— 19...
184. Robertson, Bengt, The intrapulmonary arterial pattern in norma... infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Else, Skeletal Maturation of Danish School Childr... in Relation to Height, Sexual Development, and Social Cond... tions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Revie... of the Literature and Report of Nine Cases. Sw. kr. 25.— 19...
187. Karlberg, Petter, et al., The Development of Children in a Swe... dish Urban Community. A Prospective Longitudinal Study I–V... Sw. kr. 30.— 1968
188. Meeuwisse, Gunnar W. and Mellin, Kerstin, Studies in Glucos... Galactose Malabsorption. A Clinical Study of 6 Cases and ... Genetic Study. Sw. kr. 21.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbo... Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of th... Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. [illegible], Antti, Cardiovascular Response of the Neonatal Lam... to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Disease... in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Peri... natal Mortality. 1969
194. Karvonen, Antti, Studies on the Serum Binding of Vitamin B... in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 15.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencin... Hospital Admission of Children. Sw. kr. 20.— 1969
197. Sandin, Ritva, Pseudomonas Infections in Paediatric Surgica... Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabete... Sw. kr. 30.— 1969
199. Villamil, Erkki, Tape Recordings of the Electrocardiogram i... Newborn Infants. Sw. kr. 30.— 1969
200. Snyder, Dina M., Cervinka, Joaquin, Romaine, Lydia and von Vo... André, Infant Feeding and Weaning Practices in a Rural Prein... dustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette E., Hartsock, Phyllis, Rollo, John U., Bailey... John D. and Lynch, Matthew J., Bartter's Syndrome. A Repor... of Four Cases, Including Three in One Sibship, with Comparativ... Histologic Evaluation of the Juxtaglomerular Apparatus and... Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr, L. J., Thomas, Lora N., and Rogers... Ronald R., Growth and Serum Chemical Values of Normal... Breastfed Infants. Sw. kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospa... dias. Sw. kr. 35.— 1970
204. Berg, Kristina, Adjustment in Cerebral Palsy of Body Compositi... tion, Nutrition and Physical Working Capacity at School Ag... Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Wate... Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress,* Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencepha... logram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Voldemar, Acute Head Injuries in Children. An Epidemi... ologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 35.— 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. Sw. kr. 25.— 1971

Price Swed. kr. 25.—

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 211 1971

SALICYLATE-INDUCED FOETAL DAMAGE LATE IN PREGNANCY

AN EXPERIMENTAL STUDY IN MICE

BY MARGARETA ERIKSSON

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

List of Supplements to Acta Paediatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB Uppsala, Sweden without charge.)

150. Mor, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics.* Lisbon, 1962. Edited by Bo Vahlquist. Sw kr 15.— 1963
152. Hjern, Bo and Nylander, Ingvar Acute Head Injuries in Children. Traumatology Therapy and Prognosis. Sw. kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic study Sw. kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw kr. 25.— 1964
157 Brante, G., Kaijser, K. and Ockerman, P A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr 25.— 1965
159 *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm, 1964. Edited by Y Larsson. Sw kr 25.— 1965
160. Ockerman, P A., Glycogen Storage Disease in Sweden. Sw kr. 25 — 1965
161. Peltonen, T and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw kr 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw kr 25.— 1964
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr 30.— 1965

Böttiger Margareta, Studies on Immunization with Inactivated Live Poliovirus Vaccines. Sw. kr 30.— 1966

, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., ...lectasis: A Review of 187 Cases in Children with Pulmonary Function Studies in 58. Sw kr 20.— 1966

...sson, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw kr. 35.— 1966

167 Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr 30.— 1966
168. Trojaborg, W Focal Spike Discharges in Children, Longitudinal Study. Sw kr 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw kr 30.— 1966
170. Bollmann, Marjut, Studies on Enuresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 28.— 1966
172. *Festschrift in Memory of Constantin Chevrents.* Sw. kr 35.— 1967
173. Walsh, S. Zoe, The Oesophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Pettersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr 25.— 1967
175. Hämäläinen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr 20.— 1967
177 *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen. 1967 Sw. kr. 35.— 1967
178. Ekbom?, Irina, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw kr 20.— 1968
181. Koch, Günter Lung Function and Acid-Base Balance in the Newborn Infant. Sw kr. 28.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study Sw. kr. 21.— 1968
183. Robertson, Alan F and Sprecher Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 21.— 1968
185. Andersen, Elsa, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187 Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community A Prospective Longitudinal Study I-VI. Sw kr 30.— 1968
188. Meeuwisse, Gunnar W., and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr 20.— 1969
190. Häråbäck?, P Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw kr. 30.— 1969
191. Källfelt?, Astrid, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kurvonen?, Astrid, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw kr 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 15.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw kr. 20.— 1969
197 Sandin?, Rita, Pseudomonas Infections in a Paediatric Surgical Unit. Sw kr. 20.— 1969
198. Kohl?, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw kr 30.— 1969
199 Villmann?, Heine, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Stapler?, Dora H., Cravioto, Joaquin, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette E., Hartmann, Phyllis, Bolen?, John U., Bailey John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw kr 30.— 1970
202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw kr 35.— 1970
204. Berg, Kristian, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30 — 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207 Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw kr 35.— 1970
210. Rosberg, Georg, Parental Attitudes to Pediatric Hospital Admission. Sw. kr. 21.— 1971

Price Swed. kr 25 —

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

710874

ACTA PAEDIATRICA SCANDINAVICA

Supplement 211 1971

From the Laboratory of Teratology and the Departments of Paediatrics,

Karolinska Institutet, Stockholm, Sweden

SALICYLATE-INDUCED FOETAL DAMAGE LATE IN PREGNANCY

AN EXPERIMENTAL STUDY IN MICE

BY

MARGARETA ERIKSSON

STOCKHOLM 1971

Boktryckeri AB Thule 1971
700491

CONTENTS

INTRODUCTION	5
Survey of the Literature	5
Salicylate action on the foetus	5
Teratogenic tests	7
PRESENT INVESTIGATIONS	8
Object of the Study	8
Methodological	8
Experimental procedures	8
Morphological observations	9
Biochemical measurements	9
Distribution of ^{14}C-salicylic acid	10
Results	10
Morphological observations	10
Biochemical measurements	11
Distribution of ^{14}C-salicylic acid	11
Discussion	12
Salicylate action on the foetus	12
Differences in foetal susceptibility to salicylate	13
Perinatal tests	14
Clinical implications	16
SUMMARY	17
ACKNOWLEDGEMENTS	19
REFERENCES	20

The present dissertation is a summary of the following papers.

I Larsson, K. S. & Eriksson, M. Salicylate-induced fetal death and malformations in two mouse strains. *Acta Paediat Scand* 55 569 1966

II Eriksson M. Salicylate-induced foetal haemorrhage in two mouse strains. *Acta Path Micr biol Scand* 76 164 1969

III Eriksson, M. Effect of salicylate treatment on fetal and maternal prothrombin time in the mouse. *Acta Physiol Scand* 78 39 1970

IV Eriksson, M. Salicylate-induced foetal damage during late pregnancy in mice. The modifying effect of repeated administration and dosage. *Acta Paediat Scand* 59 517 1970

V Eriksson, M. The effect of salicylate on the glycogen content of the foetal liver and heart in two strains of mice. *Acta Pharmacol et Toxicol* 29 1971 in press.

VI Eriksson, M. & Larsson, K. S. Salicylate induced foetal damage in two mouse strains. Studies on the distribution of ^{14}C-labelled salicylic acid. *Acta Pharmacol et Toxicol* 29 1971 in press.

VII Eriksson, M. Salicylate-induced foetal damage during late pregnancy in mice. A comparison between sodium salicylate, acetylsalicylic acid and salicylsalicylic acid. *Acta Pharmacol et Toxicol* 29 1971 in press.

Reference will be made to these papers using the Roman figures as listed above

INTRODUCTION

It has been known for many years that the bark, fruit and lea es of plants in the Spirea group contain a substance which will reduce fever and relieve pain (20 112) The use of these plants was recommended as early as the fourth century before Christ by Hippocrates. In the beginning of the 19th century the substance was identified as salicylic acid and by the end of the century *different deri atives of salicylic acid had* been synthesized. The most commonly used derivative nowadays, acetylsalicylic acid, was introduced into clinical therapy in 1899 Today salicylate is an indispensible drug due to its analgetic, antipyretic, anti-inflammatory and anti rheumatic activities. In addition, it is the most commonly used household drug, and the public attitude is that aspirin isn t a drug (33)

Intensive efforts ha e been made to elucidate the mechanism behind the different properties of salicylates (40 57 122) Thus salicylates have been shown to influence intermediary meta bolism and exert inhibitory effects on at least three ital groups of cellular enzymes i.e for oxidative phosphorylation, the transaminases and the dehydrogenases (see review by Smith & Smith 1966) (122) In this way salicylates in fluence oxygen consumption, carbohydrate, lipid and protein-aminoacid metabolism. Salicylates interact with the endocrine system. Large doses stimulate the intact pituitary-adrenal axis and *possibly interfere with the thyroid-function.*

Unwanted effects of therapeutic doses of sali cylate are haemorrhage and hypersensitivity (122) Toxic doses of salicylate produce a decrease in the glycogen content of liver muscle and myocardium and an increase in neutral fat in the liver and kidney (98) Acid-base distur bances and electrolyte imbalance are found as well (122) It is known that infants and children are more sensitive to salicylate than adults (41 42) however ery little is known about the susceptibility of the human foetus compared with experimental animals.

SURVEY OF THE LITERATURE

In this section, the most pertinent literature on salicylate action on the foetus will be briefly surveyed.

Salicylat action on the foetus

Reports of miscarriages in humans after salicylic acid ingestion led to the study of the effects of salicylate on foetal rabbits by Butz in 1893 (12) This study had several disadvantages but nevertheless gave rise to warnings in pharma cological text-books (34 63) In 1948 Jackson reported salicylate to have no damaging effect on foetal development in mice and rabbits (63) *However since 1959 salicylate has been shown* to induce malformations in most animal species (see review by Larsson 1970) (74) A few case reports suggesting a possible relation between the ingestion of salicylate and human foetal damage have been published (13, 43 109 114) Many reviews on foetal hazards of drugs also warn that salicylate can give rise to neonatal haemorrhage (4 90 104 141)

A review of the published literature on the effect of salicylate on prenatal development shows that only a few studies have been per

formed during preimplantation stages. Salicylic acid given to mice, rats and rabbits has been shown to be transferred from maternal circulation to uterine secretion early in pregnancy (70) and to penetrate the rabbit blastocyst and change its protein profile (69) Abnormal blastocysts, but normal-sized litters were found in rabbits (116)

Many different types of malformations have been described after salicylate treatment during the organogenetic period. Skeletal anomalies especially of vertebrae and ribs have often been induced in mice rats and rabbits (2, 5 28 29 75 135) Cleft lip and cleft palate have been found in mice and rats (5 77 129 135) Cardiovascular central nervous and other gross defects have been induced in rats (5 127 135) Vessel anomalies have been found in mice (76 77) and haemorrhage in the cochlea of guinea pigs (93) Abortions and a foetus with multiple malformations were found after treatment of rhesus monkeys (138) Reduced foetal weight has been noticed (5 28 44) A general finding in most studies is a high rate of foetal death and resorption There are also a few studies where no damaging effect of salicylate treatment has been demonstrated (32, 63 131)

The mechanism behind the teratogenic action of salicylate also has been discussed and investigated A direct toxic effect on the foetal cells has been proposed and the uncoupling effect on oxidative phosphorylation has been discussed (54 67) Dinitrophenol a well-known uncoupling agent however has failed to produce any anomalies under the same conditions (54 67) Histochemical studies on foetal tissue have not shown alterations in different enzyme activities known to be inhibited by salicylat (54) Salicylate induced hypoglycaemia has received special attention following the demonstration in rat that the foetal damaging effects of sodium salicylate were potentuated by the hypoglycaemia inducing drug arbutamide (6) The well known ability of salicylates to reduce liver glycogen content in adults has also been discussed (65 67) Maternal weight is often reduced following salicylate treatment (5 66, 115 135) as well as food consumption (115) Moreover high protein diet has a tendency to reduce the toxic effects of salicylate (17) The teratogenic effect of salicylate is enhanced by the stress-situation of maternal immobilization (53) This combined effect of salicylate treatment and immobilization is prevented by the central nervous depressant sodium pentobarbital and chlorpromazine (55) and augmented by reserpine treatment (56) As a result of these studies disturbed catecholamine metabolism was suggested as an important teratogenic factor Electrolyte imbalance has been pointed out as a peripheral effect of this salicylate-induced maternal stress phenomena for the number of anomalies is augmented by administering ammonium chloride to the mother and decreased by administering sodium bicarbonate (54) Salicylate-induced inhibition of the synthesis of acid sulpho-mucopolysaccharide (an important factor in ground substance) has been suggested to underlie skeletal malformations (64 75) The possibility of a haemorrhagic effect of salicylate in foetuses has also been discussed (17 63) but not proven until recently (13)

Different derivatives of salicylate were used in the above mentioned studies, most frequently sodium salicylate and acetylsalicylic acid. The most common route of administration was oral, in the diet or through gastric tube. The next most common route was subcutaneous injection. Rats and mice were used in most studies while rabbits were used in only a few Acetylsalicylic acid also has been tested in monkeys (32 138) and sodium salicylate in avian embryos (71) The dose used in mice and rats varied between 100 and 600 mg/kg The minimum teratogenic dose for sodium salicylate in rats has been calculated to be 300 mg/kg (6) Drug administration varied from a single dose to repeated doses throughout pregnancy

In a few of the above mentioned studies salicylate was administered throughout pregnancy as a part of the diet (28, 115) The end result was an increased incidence of foetal resorptions. In a chronic toxicity study over five generations acetylsalicylic acid reduced the rearing of young.

but not more than other analgetic drugs (140)

In comparison with the numerous experimental studies during the organogenetic period only a few studies relating exclusively to the foetal period can be found. Decrease in litter size and decrease in viability of the newborns have been found as well as maternal neglect (115) A low dose of acetylsalicylic acid in the diet of pregnant rats from day 15 to term resulted in an increased tolerance of the newborns to this drug as measured by the LD 50 (136) The mechanism behind this was suggested to be a stimulation of hepatic detoxifying enzymes.

Teratogenic tests

With the increasing development of new drugs a need for guidelines for toxicity studies arose. In the early recommendations the study of reproduction was included as a possible part of a chronic toxicity test (7 ??) Before 1961 teratological studies were mostly devoted to the development of various methods for experimental production of congenital malformations.

Since 1961 when thalidomide first was suspected of being teratogenic in man (16, 80) discussions have been focused on the design of a teratogenic test for the safety evaluation of drugs for human use (23 36 50 130) The early guidelines for teratogenic tests stressed the possibility of inducing foetal damage during the organogenetic period (23 78 130) Lately however the vulnerability of the foetus during the perinatal period has received attention and special tests for this part of gestation have been recommended (31 49 97)

OBJECT OF THE STUDY

A review of the literature of the last decade emphasizes the increased interest and research in the action of drugs on prenatal development. Earlier studies were devoted primarily to the production of malformations during the organogenetic period, with little interest evident in the late foetal period. However the last trimester of gestation is a period of rapid metabolic maturation with considerable risk for fatal interference.

Consequently it seemed expedient to study in more detail different aspects of drug action in the last third of gestation with special reference to test procedures for adverse effect on the foetus. Sodium salicylate seemed to be a suitable drug for this purpose since its effects have been studied in detail during the organogenetic period. The aims of the present experimental investigations in mice (reported in papers I—VII) were

1. To study the morphological effects of sodium salicylate at different stages of gestation, especially the last third.
2. To study the biochemical effects of sodium salicylate concerning the prothrombin time and liver and heart glycogen content in the foetus.
3. To study the modification of the foetal damaging effect of sodium salicylate by some genetic and environmental factors.
4. To study the distribution of salicylic acid in mother and foetus under different conditions, using isotope techniques.
5. To test different salicylate derivatives in late pregnancy in relation to earlier studies and drug test recommendations.

METHODOLOGICAL

Experimental procedures

In the present investigations mice of two strains were used. A/Jax mice were kept and inbred in the laboratory since 1958 (7) and CBA mice were obtained from Institute of Genetics, University of Stockholm, and housed in our laboratory for at least 10 days before use. The mice were used at the age of [illegible]— months. They were fed standardized diets from commercial suppliers and water *ad libitum*.

Pregnant primiparous animals were used. They had been mated over night and the day of vaginal plug was denoted as day zero of pregnancy. From day 9 of gestation the animals were weighed and observed daily. The animals were sacrificed by cervical dislocation at different times as described below.

All test substances were administered at 10 a.m. The substances given were sodium salicylate dissolved in distilled water or 1 % CMC (carboxymethyl-cellulose), acetylsalicylic acid, and salicylsalicylic acid in 1 % CMC, coumarin (Waran®) in saline and pentobarbital (Nembutal®) in distilled water. Sodium salicylate in different concentrations and coumarin were

given as i.m. and pentobarbital as i.p. injections of 0.1 ml/20 g body-weight. The substances dissolved in CMC were given through a stomach tube (0.1 ml/10 g).

The effect of a single dose of 10 mg/20 g body weight of sodium salicylate was studied at different stages from day 9 to 17 of gestation in the A/Jax and CBA strains (I). All animals were sacrificed on day 18 of gestation. In a more detailed morphological study on day 16, 17 and 18 of gestation the animals were sacrificed after shorter intervals, from 2 to 24 hours after injection (II). Comparisons of foetal damaging effects of sodium salicylate, acetylsalicylic acid and salicylsalicylic acid were made on day 17 of gestation in the A/Jax strain (VII). The treated animals were killed and examined 4 and 24 hours after drug administration. Three different doses of sodium salicylate, selected after determination of LD 50, were tested on day 17 of gestation, all surviving females were sacrificed after 24 hours (IV).

In order to study the effect of drug pretreatment on salicylate induced damage on day 17 of gestation in the A/Jax strain either sodium salicylate (3 mg/20 g or 10 mg/20 g) or pentobarbital (Nembutal®) (1.5 mg/20 g) was given on day 15 and 16 followed by sodium salicylate (10 mg/20 g) on day 17 of gestation (IV). The dose of pentobarbital was narcotic for the mice used. The animals were sacrificed on day 18 of gestation.

Prothrombin time was studied on day 17 of gestation at 4, 8, 12 and 24 hours after treatment with sodium salicylate in the A/Jax strain (III). Untreated animals of the same gestational age served as controls. One group of animals was given coumarin (Waran®) (1 mg/20 g) on day 17 and sacrificed after 8 hours. The animals were anesthetized with pentobarbital (1.5 mg/20 g) and a double sample of blood was taken through a cut in the tail. Foetal blood was taken from a cut in the neck.

Glycogen concentration was determined 4, 8 and 24 hours after treatment on day 17 of gestation with 10 mg or 3 mg/20 g sodium salicylate in both the A/Jax and CBA strains (V). Samples for determination were taken from foetal liver and in some animals from maternal liver or foetal heart. Following oral administration of three derivatives of salicylate, foetal liver glycogen content was determined 4 hours afterwards in the A/Jax strain (VII). Untreated animals of the same gestational age served as controls.

The distribution of ^{14}C-labelled salicylic acid given with sodium salicylate as carrier on day 17 of gestation was studied in maternal liver and blood and in the whole foetus of A/Jax and CBA mice (VI). Samples were obtained for liquid scintillation counting at 1/2, 1, 2, 4 and 8 hours after administration of the labelled salicylate. A similar study was carried out in A/Jax mice after pretreatment with sodium salicylate (3 mg/20 g) or pentobarbital (1.5 mg/20 g) on days 15 and 16. Samples were taken 1/2, 1, 2 and 4 hours after ^{14}C-salicylate injection on day 17. Labelled salicylate distribution was also studied in day 14 A/Jax and CBA mice 1/2 and 4 hours after injection and in adult nonpregnant A/Jax mice 1/2, 2 and 4 hours after administration.

Morphological observations

The mothers were observed after treatment for the occurrence of premature births. The foetuses were removed for examination and records made of foetal resorptions and death. Early foetal resorptions, which evidently had occurred before treatment of the mother, are not included in the tables in papers II—VII. Living foetuses were examined for external malformations and vessel anomalies (I, IV), superficial haemorrhage (II—VII) and whenever possible for liver haemorrhage and gastric haemorrhage (IV, VII). Skeletal malformations were looked for (I) after Alizarin red staining (38). Histological examination of the foetal liver was performed after fixing the foetuses in Bouin's fluid, sectioning at 7 μ and staining with Hematoxylin-eosin (II).

Biochemical measurements

Prothrombin time was determined in a two stage procedure with freeze dried reagents (III) as

PRESENT INVESTIGATIONS

OBJECT OF THE STUDY

A review of the literature of the last decade emphasizes the increased interest and research in the action of drugs on prenatal development. Earlier studies were devoted primarily to the production of malformations during the organogenetic period, with little interest evident in the late foetal period. However the last trimester of gestation is a period of rapid metabolic maturation with considerable risk for fatal interference.

Consequently it seemed expedient to study in more detail different aspects of drug action in the last third of gestation with special reference to test procedures for adverse effect on the foetus. Sodium salicylate seemed to be a suitable drug for this purpose since its effects have been studied in detail during the organogenetic period. The aims of the present experimental investigations in mice (reported in papers I—VII) were

1. To study the morphological effects of sodium salicylate at different stages of gestation, especially the last third.
2. To study the biochemical effects of sodium salicylate concerning the prothrombin time and liver and heart glycogen content in the foetus.
3. To study the modification of the foetal damaging effect of sodium salicylate by some genetic and environmental factors.
4. To study the distribution of salicylic acid in mother and foetus under different conditions, using isotope techniques.
5. To test different salicylate derivatives in late pregnancy in relation to earlier studies and drug test recommendations.

METHODOLOGICAL

Experimental procedures

In the present investigations mice of two strains were used. A/Jax mice were kept and inbred in the laboratory since 1958 (7) and CBA mice were obtained from Institute of Genetics, University of Stockholm, and housed in our laboratory for at least 10 days before use. The mice were used at th age of 3—5 months. They were fed standardized diets from commercial suppliers and wate *ad libitum*.

Pregnant primiparous animal ere used. They had been mated over night a d the day of vaginal plug was denoted as day zero of pregnancy. From day 9 of gestation the animals were weighed and observed daily. The animals were sacrificed by cervical dislocation at different times as described below.

All test substances were administered at 10 a.m. The substances given were sodium salicylate dissolved in distilled water or 1 % CMC (carboxymethyl-cellulose) acetylsalicylic acid, and salicylsalicylic acid in 1 % CMC, coumarin (Waran®) in saline and pentobarbital (Nembutal®) in distilled water. Sodium salicylate in different concentrations and coumarin were

given as i.m. and pentobarbital as i.p. injections of 0 1 ml/20 g body weight. The substances dissolved in CMC were given through a stomach tube (0 1 ml/10 g)

The effect of a single dose of 10 mg/20 g body weight of sodium salicylate was studied at different stages from day 9 to 17 of gestation in the A/Jax and CBA strains (I) All animals were sacrificed on day 18 of gestation. In a more detailed morphological study on day 16 17 and 18 of gestation the animals were sacrificed after shorter intervals, from 2 to 24 hours after injection (II) Comparisons of foetal damaging effects of sodium salicylate, acetylsalicylic acid and salicylsalicylic acid were made on day 17 of gestation in the A/Jax strain (VII) The treated animals were killed and examined 4 and 24 hours after drug administration. Three different doses of sodium salicylate, selected after determination of LD 50 were tested on day 17 of gestation, all surviving females were sacrificed after 24 hours (IV)

In order to study the effect of drug pretreatment on salicylate induced damage on day 17 of gestation in the A/Jax strain either sodium salicylate (3 mg/20 g or 10 mg/20 g) or pentobarbital (Nembutal®) (1.5 mg/20 g) was given on day 15 and 16 followed by sodium salicylate (10 mg/20 g) on day 17 of gestation (IV) The dose of pentobarbital was narcotic for the mice used. The animals were sacrificed on day 18 of gestation.

Prothrombin time was studied on day 17 of gestation at 4 8 12 and 24 hours after treatment with sodium salicylate in the A/Jax strain (III) Untreated animals of the same gestational age served as controls. One group of animals was given coumarin (Waran®) (1 mg/20 g) on day 17 and sacrificed after 8 hours. The animals were anesthetized with pentobarbital (1.5 mg/20 g) and a double sample of blood was taken through a cut in the tail Foetal blood was taken from a cut in the neck.

Glycogen concentration was determined 4 8 and 24 hours after treatment on day 17 of gestation with 10 mg or 3 mg/20 g sodium salicylate in both the A/Jax and CBA strains (V) Samples for determination were taken from foetal liver and in some animals from maternal liver or foetal heart. Following oral administration of three derivatives of salicylate foetal liver glycogen content was determined 4 hours afterwards in the A/Jax strain (VII) Untreated animals of the same gestational age served as controls.

The distribution of ^{14}C-labelled salicylic acid given with sodium salicylate as carrier on day 17 of gestation was studied in maternal liver and blood and in the whole foetus of A Jax and CBA mice (VI) Samples were obtained for liquid scintillation counting at 1/2 1 2 4 and 8 hours after administration of the labelled salicylate A similar study was carried out in A/Jax mice after pretreatment with sodium salicylate (3 mg/20 g) or pentobarbital (1.5 mg/20 g) on days 15 and 16 Samples were taken 1/2, 1 2 and 4 hours after ^{14}C-salicylate injection on day 17 Labelled salicylate distribution was also studied in day 14 A/Jax and CBA mice 1/2 and 4 hours after injection and in adult nonpregnant A/Jax mice 1/2, 2 and 4 hours after administration.

Morphological observations

The mothers were observed after treatment for the occurrence of premature births. The foetuses were removed for examination and records made of foetal resorptions and death. Early foetal resorptions, which evidently had occurred before treatment of the mother are not included in the tables in papers II—VII Living foetuses were examined for external malformations and vessel anomalies (I IV) superficial haemorrhage (II—VII) and whenever possible for liver haemorrhage and gastric haemorrhage (IV VII) Skeletal malformations were looked for (I) after Alizarin red staining (38) Histological examination of the foetal liver was performed after fixing the foetuses in Bouin's fluid sectioning at 7 μ and staining with Hematoxylin-eosin (II)

Biochemical measurements

Prothrombin time was determined in a two stage procedure with freeze dried I) as

described in detail by Norén (100) The time intervals were the same as used for prothrombin determination on human blood. Whole blood was used as only very small amount of blood could be obtained.

Glycogen isolation and determination was performed by a method slightly modified from Seifter *et al.* (118) Isolation was made by boiling with potassium hydroxide and precipitation with ethanol (V VII) Determination was performed with anthrone reagent. These procedures have been compared to others and found suitable for determination of glycogen in micro amounts of tissue (83) For practical reasons the livers could not be weighed immediately but were weighed frozen just before analysis. In these studies glycogen values are consequently expressed as µg/mg frozen tissue.

Microsomal hydroxylating enzymes in maternal liver were studied after isolation of the liver microsomes (IV) as described by Ernster *et al* (46) The oxidative demethylation of aminopyrine, NADPH cytochrome *c* reductase and the amount of cytochrome P-450 were assayed as described by Dallner (35) and Orrenius & Thor (101) The values were calculated in relation to the protein content which was measured according to the method of Lowry *et al* (86)

Distribution of ^{14}C-salicylic acid

^{14}C-salicylic acid (1 µC/20 g) was injected with sodium salicylate as a carrier (10 mg/20 g) to induce foetal damage (VI) Liquid scintillation counting was used to determine the radioactivity in the maternal liver and blood, and in the whole foetus. The liver and foetus were homogenized in ethanol and the dry powder was digested in a solution of perchloric acid and hydrogen peroxide as described by Mahin & Lofberg (88) Scintillation fluid was added just prior to counting

Statistical analysis was performed by "Student's *t* test.

RESULTS

Morphological observations

Foetal death incidence following sodium salicylate administration was found to increase directly with increased age of the foetus at the time of injection. The highest incidence of foetal death and resorption (75 %) was found after a single dose of sodium salicylate on gestation day 15 or 17 The lowest incidence (20 %) occurred after a single injection on day 9 (I) The high foetal death rate was confirmed in studies II through VII although the incidence varied.

The more detailed study on day 17 of gestation revealed the first evidence of foetal death at 4 to 8 hours following treatment (II) Subsequently the frequency increased. On the other hand, on day 16 of gestation the maximum death rate had been reached by 8 hours. On day 18 of gestation foetal death could not be induced before 8 hours and by 4 hours all females had delivered.

A strain difference was found as the incidence of foetal death in the CBA strain was always lower than in the A/Jax strain after sodium salicylate treatment (I II V) Matings between A/Jax females and CBA males gave intermediate results. Matings between CBA females and A/Jax males did not increase the foetal death rate compared to the CBA strain (I)

Two salicylate derivatives, acetylsalicylic acid and salicylsalicylic acid, induced an increased death incidence late in pregnancy When these substances were given in a dose relative to the LD 50 acetylsalicylic acid seemed to be the more toxic of the two drugs (VII)

Foetal haemorrhage located subcutaneously on the back and head was observed after treatment on day 16 and 17 (II) Four hours after treatment on day 17 haemorrhage could be found in about one third of all living foetuses. In all subsequent studies these were found in

varying number of foetuses (III—VII) The haemorrhages varied in extent from petechiae to confluencing haematomas.

Subcapsular liver haemorrhage was found in about one half of the foetuses with superficial haemorrhage (II—VII) These were found by 4 hours as well. A few cases of isolated liver haemorrhages were found. Histological examination of these foetal livers showed haemorrhagic and necrotic areas (II) Gastric haemorrhage, located in the submucosa was also observed (IV VII) Salicylate induced haemorrhages were found in both strains at about the same rate (II)

Premature birth occurred after treatment on day 17 of gestation. The incidence varied from 5 of 11 to 2 of 20 treated (I IV) When treatment was given on day 18 all females gave birth within 24 hours (II) in contrast to untreated A/Jax mice, which delivered on day 19 (45) The incidence of premature delivery was the same in the CBA and A/Jax strains.

Malformations of vertebrae and ribs were found after salicylate administration on day 9 (I) These were induced in both strains but at a higher rate in the A/Jax strain.

Vessel anomalies, histologically characterized by dilated sacs as described earlier (76 77) were observed after salicylate treatment on day 13 and 15 (I IV)

Biochemical measurements

Prothrombin concentration was lower in foetal blood than in maternal blood in untreated A/Jax mice on day 17 of gestation (III) The foetal prothrombin time decreased from day 17 to 18. Salicylate treatment did not change the prothrombin time in the mother or in foetuses without visible haemorrhage. However in foetuses with induced haemorrhage the prothrombin time was significantly increased at 8 and 12 hours after injection but by 24 hours after treatment there was no difference. With coumarin treatment a prolongation of prothrombin time could be observed in both maternal and foetal blood. However no haemorrhages could be seen in either foetuses or mother

Glycogen content in the foetal liver and to a lesser degree in the foetal heart, increased during day 1 of gestation in untreated mice (V VII) On day 18 they both exceeded these of the mother Maternal liver glycogen was significantly reduced 4 hours after salicylate treatment (10 mg/20 g) and returned to the control values by 8 hours. In unaffected foetuses of both strains liver glycogen was reduced at 4 and 8 hours but not at 24 hours after treatment. Foetuses with haemorrhages generally had a lower liver glycogen content than unaffected foetuses of the same group With the lower dose of salicylate (3 mg/20 g) all foetuses were unaffected and the foetal liver glycogen was reduced at 4 hours but not at 8 hours. Foetal heart glycogen was decreased 4 8 and 24 hours after treatment in foetuses with haemorrhages but not in unaffected ones.

The other salicylate derivatives, acetylsalicylic acid and salicylsalicylic acid, significantly decreased foetal liver glycogen 4 hours after oral administration (VII) The suspension of carboxymethyl-cellulose also reduced the glycogen content.

Microsomal hydroxylating enzyme activity for aminopyrine demethylation in the maternal liver increased following pentobarbital treatment on days 15 and 16 of gestation (IV) The same pretreatment with high and low salicylate doses had no effect. No change was observed for NADPH cytochrome *c* reductase or cytochrome P-450

Distribution of ^{14}C-salicylic acid

A great individual difference in handling of ^{14}C-labelled salicylic acid was noted in A/Jax and CBA females (VI) No difference could be noted among nonpregnant, day 14 or 17 pregnant animals in this respect. Pretreatment with low dose of sodium salicylate or a narcotic dose of pentobarbital had no effect on the distribution of labelled salicylic acid. Radioactivity in

the maternal liver was not significantly changed during the 8 hours studied. Maternal blood radioactivity decreased slowly and at 8 hours it had reached about 40 % of the initial value. Foetal radioactivity also decreased slowly during the first 4 hours and at 8 hours it had reached about one-half of the initial value. No difference could be found at this time between unaffected foetuses and the haemorrhagic or dead ones. In the CBA strain there was a tendency toward a higher initial radioactivity than in the A/Jax strain but no clear strain difference in the distribution of ^{14}C-labelled salicylic acid and its metabolites could be found.

DISCUSSION

The results obtained merit discussion from some different points of view. Thus it is of great interest to evaluate the relationship between salicylate-induced morphological and biochemical foetal damage late in pregnancy. An indication can be made by comparing similar damages induced by other agents, but also by comparing the salicylate effect known from adults with those obtained in the foetus. Another question is the mode in which the salicylate induced foetal da ... effect is modified by genetic factors and by drug pretreatment. From a more practical point of view the results from the present studies indicate that sodium salicylate can be used as a model substance in a discussion for designing new drug tests in the perinatal period.

Salicylate action on the foetus

Foetal haemorrhages, located in skin, liver and stomach were one of the most constant findings following salicylate treatment late in pregnancy in both mouse strains (II). It is interesting to note that the mothers, on the other hand, never showed haemorrhages. Drugs such as coumarin, quinine, thiazide and phenobarbital given to the mother during pregnancy have in some cases been shown to cause haemorrhages in the foetus or newborn (3 15 89 95 110). Another reason for foetal and newborn haemorrhages found at autopsy (58, 91) is anoxia, often associated with degenerative changes in the liver (58 132). This type of damages was also observed in the mouse foetus following salicylate treatment (II). The underlying mechanism of the induced heamorrhages has been suggested to be thrombocytopenia (89 110) and/or a coagulation defect due to a depression of some of the coagulation factors (3 60 95).

Salicylate has also been stated to cause neonatal haemorrhage (4 90 104 141) although experimental studies have not earlier been available to support this statement. In patients dying from salicylate intoxication haemorrhages have been a common finding (122). Haemorrhages also have been induced in the adult following therapeutic doses of salicylate (51). Many underlying mechanisms have been proposed and discussed such as thrombocytopenia, platelet disorders, capillarily fragility and hypoprothrombinaemia or a combination of these (47 51 84 108 137).

Foetuses and newborns have a lower prothrombin concentration than adults (24 143) which was confirmed in the A/Jax mice (*III*). A further decrease of the originally low foetal prothrombin value could be surmised to cause the salicylate-induced haemorrhages. The induced prothrombin reduction in the foetuses with haemorrhages, however could hardly be the only underlying mechanism, as coumarin-treated animals had the same low values without showing any sign of haemorrhage. Platelet dysfunction and diminished factor XII activity have recently been demonstrated in newborns of mothers who had taken aspirin during the week prior to birth (13).

The hypoprothrombinaemic action of salicylate has been suggested to be due to its structural similarity to coumarin and may be mediated

through a direct action on prothrombin synthesis (27 84) Prothrombin is synthesized in the liver (8) and its foetal concentration depends on hepatic maturity since a placental barrier to coagulation factors supposedly exists (21) This opinion has been challenged by others (61) In adults a large parenteral dose of sodium salicylate has been shown to induce minor biochemical and structural changes in the liver (18) and now foetal liver damage as documented by haemorrhage and necrosis have been induced in the same way (II) As mentioned before one of the mechanisms underlying salicylate-induced haemorrhage is hypoprothrombinaemia which is easily induced in combination with existing liver damage (9) The question then arises whether or not the foetal hypoprothrombinaemia could be a sign of general liver damage. This liver damage would probably be reflected by an impairment of other functions of the liver *e.g.* liver glycogen metabolism (11) In fact salicylate is known to reduce liver glycogen in adults (122, 124) The mechanisms underlying this have been postulated to be increased glycogenolysis mediated by adrenal medullary stimulation and decreased glycogen synthesis (122)

In the last part of gestation the foetus is known to accumulate glycogen especially in the liver and heart (105 119 120) This accumulation of glycogen in the foetal liver and heart has in rodents been shown to be dependent on corticosteroids (19 48, 107) A single dose of sodium salicylate has, moreover been shown to stimulate the foetal rat adrenal cortex (79) Foetal liver glycogen has been shown to be reduced by chlorpromazine (113) and probably anoxia (87) Foetal heart glycogen can be reduced by sodium pentobarbital treatment (39) and anoxia (87) Even small doses of salicylate which with morphological methods seem to be without harm, reduced foetal liver glycogen concentration (V) The foetal heart glycogen, however was only reduced following high salicylate doses and in foetuses with haemorrhages. It has been suggested that anaerobic glycogenolysis of the above mentioned glycogen stores, especially in the hearts, increases the ability of newborns to survive during anoxia (62, 94) Moreover a direct relationship has been found between foetal and newborn heart glycogen content and the anoxic survival time in different species (37 121) Administration of glucose to rabbit mothers during labour increases the foetal heart glycogen content and prolongs heart activity under anoxic conditions (52) The same treatment has been shown to correct foetal bradycardia in humans and dogs (111 128)

The fact that a low dose of salicylate reduces foetal liver glycogen concentration but does not cause foetal haemorrhage and death gives rise to speculation that a decrease in foetal glycogen is an early transitory effect induced by salicylate (I—VII) The CBA strain, which is less susceptible to some kind of induced foetal damage (73 I II V) reacts to high doses of salicylate with reduction in foetal liver glycogen and foetal haemorrhage but not with increased foetal death rate. Treating the A/Jax strain with high doses of salicylate decreases foetal liver glycogen concentration, induces foetal haemorrhage and causes a high foetal death rate (I II V) In all studies liver glycogen reduction and foetal haemorrhage are found prior to the time when foetal death occurs. The above mentioned facts suggest a relationship between reduced foetal liver glycogen foetal haemorrhage and foetal death

Differences in foetal susceptibility to salicylate

Most pharmacokinetic studies of salicylate have been performed in man (82 122) In man salicyluric acid is formed as a first order and glucuronides and free salicylic acid eliminated as a zero order process (82) In the mouse glucuronides and salicyluric acid can be formed (125)

In studies on the distribution of drugs between mother and foetus isotope techniques such as autoradiography (68, 133) or liquid scintillation counting (81 92) have been used. Often only the total radioactivity is measured and one must be aware that in this way it is not possible

to distinguish between the administered substance and its metabolites. The distribution of labelled sodium salicylate in adult male mice has been investigated using the liquid scintillation counting technique (125). A long lasting radioactivity in the liver was found. It is interesting to note that the foetuses showed as high a radioactivity as the maternal liver (VI).

A marked individual variation in response to salicylate treatment was noted with the techniques used in the present experiment (VI). This may help to explain the difference in response among litters, which is well-known in teratological studies. Environmental factors can stimulate or inhibit drug metabolizing enzymes (30). Drugs, e.g. barbituric acid derivatives, given to the mother late in pregnancy have also been shown to stimulate the activity of foetal enzymes (25, 103). This stimulation only takes place late in pregnancy (59). Acetylsalicylic acid given during the last third of gestation in rats decreased the neonatal susceptibility of this drug (136). Moreover, it has been shown that pretreatment with low doses of sodium salicylate and narcotic doses of pentobarbital protects against the foetal damaging action of a high dose of sodium salicylate (IV). Pentobarbital, but not sodium salicylate, increased the activity of maternal hydroxylating enzymes (IV). However, no increase in the rate of disappearance of ^{14}C-labelled salicylic acid and possible metabolites could be found after pretreatment with either salicylate or pentobarbital (VI).

In this study two strains of mice with different teratogenic susceptibility both during the organogenetic period (73, 75) as well as the last third of gestation have been used (I, II, V). This difference could be due to differing response of the tissue per se or differing concentration of the active substance in the tissue. Drug metabolism has been shown to vary between mouse strains due to an inherited difference present already in newborns (142). Previous studies have shown differences in metabolism and/or tissue binding to underlie difference in foetal susceptibility to cortisone (81). In this study no such difference could be found (VI).

However, one must be aware of the fact that the method used here and in most other studies, measures the total radioactivity and cannot distinguish between active and detoxified substances. The extent of plasma protein binding of salicylate has been shown to vary considerably between different species (126). Moreover, protein binding of human foetal plasma to salicylate changes during gestation and shows a gradient to maternal plasma binding capacity (10).

Perinatal tests

In 1966 a WHO group reviewed the scientific bases of methods then available for testing drugs for teratogenicity (139). Moreover, they attempted to evaluate whether or not the teratogenic effects seen in animals could be extrapolated to man. Suggestions for testing procedures were made with full awareness of the limitations involved. Many countries now have presented their own recommendations for teratology tests (26, 31, 49, 97).

It is interesting to note that in FDA's "Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use" (1966) perinatal and postnatal studies are recommended in addition to the teratological studies (49). The purpose being "to study the effects of a drug administered during the last third of pregnancy and the period of lactation. Studies should delineate the effects of the drug on late fetal development, labor and delivery, lactation, neonatal viability and growth of the newborn". However, compared with the numerous investigations on the influence of drugs during the organogenetic period few studies have been performed during the last part of gestation. Our observation that salicylate was not only teratogenic in the classic sense in mice, but that it also produced a high incidence of foetal death when given late in gestation, led us to initiate detailed studies on its foetal damaging effect in the perinatal period (I). The design of perinatal studies will be discussed in comparison with the design of teratological studies and in view of experiences

gained using salicylate compounds as model substances.

When judging the drug effect in perinatal studies, emphasis should be placed on observations of labour, delivery and duration of gestation (49). Biochemical and functional derangements can be suspected from the known pharmacological action of the drug, and should be looked for (159). However, no concrete examples or recommendations are given in the guidelines. Sodium salicylate has been shown to induce morphological damage, *e.g.* foetal haemorrhage and death as well as biochemical damage, *e.g.* reduction of foetal prothrombin and glycogen (I—VII). Premature birth has also followed salicylate administration on day 17 of gestation (45, I, II, IV).

In teratological studies the duration of drug administration is recommended to cover the entire gestation period (31), or at least the organogenetic period (days 6 to 15 in mice) (26, 78, 97). In perinatal and postnatal studies the drug is recommended to be given during the final third of gestation (from day 15 in mice) and during the lactation period (49, 97). In the present studies the results of treatment during the perinatal period have been observed either as an effect before birth or as an effect upon the time of delivery (I—VII, 45). Thus, only part of the test period was covered. Some guidelines point to the problem of enzyme induction following repeated drug administration (26, 159). This is discussed in detail on page 14. Enzyme induction is of special interest following drug testing late in pregnancy for this is a time during which enzyme induction might also occur in the foetal liver (156). In one of the studies (IV) it was clearly shown that pretreatment with small doses of sodium salicylate, or narcotic doses of pentobarbital, protected against salicylate induced foetal damage late in pregnancy. However, neither enzyme studies nor isotope experiments have thus far revealed an explanation for the observed protective effect (VI). Thus, it seems justified to administer the substance for a short period in perinatal studies as well as in teratological studies.

At least two doses are recommended for the teratologic test procedures. The highest dose should be the maximum tolerated by the mother selected in relation to the LD 50 or ED 50 (26, 49, 97, 159). The lowest dosage should take into account the proposed therapeutic dose and should be some multiple of this (49, 97). It has been pointed out that the dose will not necessarily be the same in the teratogenic and the perinatal test (49). Dose-response curves can be constructed for the foetal damaging effect as well as for other toxic properties of a drug (17, 85, 117). The curve and its shape, however, can vary considerably (117). In a study on cytostatics it was shown that there is no relation between the LD 50 dose and the teratogenic dose (96). The foetal mortality range for acetylsalicylic acid in rats has been shown to be very narrow (17). The empirically found teratogenic dose in mice induced damage during the last third of gestation and seemed suitable for use during this period (I). A lower dose, corresponding to one fifth of the LD 50, was found to reduce foetal liver glycogen but did not induce death or visible damages (IV, V).

The drug being tested should be given by the same route that it would be administered in clinical use, *i.e.* mostly orally (26, 31, 49, 97, 159). The same dose of sodium salicylate, in relation to LD 50, on day 17 of gestation gave similar results when administered intramuscularly or through a gastric tube (VII).

It is a well-known fact that teratogenic susceptibility differs between species, and even among strains of the same species. For example, the teratogenic action of thalidomide varies between different species (123). The rate of cortisone-induced cleft palate differs between mouse strains (65). In this study two mouse strains were chosen with known differences in susceptibility during the organogenetic period (73, 75). It is interesting to note that they showed these same differences in susceptibility in the perinatal studies (I, II, V). The possible mechanism behind this strain difference has been discussed earlier on page 14.

to distinguish between the administered substance and its metabolites. The distribution of labelled sodium salicylate in adult male mice has been investigated using the liquid scintillation counting technique (125). A long lasting radioactivity in the liver was found. It is interesting to note that the foetuses showed as high a radioactivity as the maternal liver (VI).

A marked individual variation in response to salicylate treatment was noted with the techniques used in the present experiment (VI). This may help to explain the difference in response among litters which is well known in teratological studies. Environmental factors can stimulate or inhibit drug metabolizing enzymes (30). Drugs, *e.g.* barbituric acid derivatives given to the mother late in pregnancy have also been shown to stimulate the activity of foetal enzymes (25, 103). This stimulation only takes place late in pregnancy (59). Acetylsalicylic acid given during the last third of gestation in rats decreased the neonatal susceptibility of this drug (136). Moreover, it has been shown that pretreatment with low doses of sodium salicylate and narcotic doses of pentobarbital protects against the foetal damaging action of a high dose of sodium salicylate (IV). Pentobarbital, but not sodium salicylate, increased the activity of maternal hydroxylating enzymes (IV). However, no increase in the rate of disappearance of ^{14}C-labelled salicylic acid and possible metabolites could be found after pretreatment with either salicylate or pentobarbital (VI).

In this study two strains of mice with different teratogenic susceptibility both during the organogenetic period (73, 75) as well as the last third of gestation have been used (I, II, V). This difference could be due to differing response of the tissue *per se* or differing concentration of the active substance in the tissue. Drug metabolism has been shown to vary between mouse strains due to an inherited difference present already in newborns (142). Previous studies have shown differences in metabolism and/or tissue binding to underlie differences in foetal susceptibility to cortisone (81). In this study no such difference could be found (VI).

However, one must be aware of the fact that the method used here and in most other studies, measures the total radioactivity and cannot distinguish between active and detoxified substances. The extent of plasma protein binding of salicylate has been shown to vary considerably between different species (126). Moreover, protein binding of human foetal plasma to salicylate changes during gestation and shows a gradient to maternal plasma binding capacity (10).

Perinatal tests

In 1966 a WHO group reviewed the scientific bases of methods then available for testing drugs for teratogenicity (139). Moreover, they attempted to evaluate whether or not the teratogenic effects seen in animals could be extrapolated to man. Suggestions for testing procedures were made with full awareness of the limitations involved. Many countries now have presented their own recommendations for teratology tests (26, 31, 49, 97).

It is interesting to note that in FDA's "Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use" (1966) perinatal and postnatal studies are recommended in addition to the teratological studies (49). The purpose being "to study the effects of a drug administered during the last third of pregnancy and the period of lactation. Studies should delineate the effects of the drug on late fetal development, labor and delivery, lactation, neonatal viability and growth of the newborn". However, compared with the numerous investigations on the influence of drugs during the organogenetic period few studies have been performed during the last part of gestation. Our observation that salicylate was not only teratogenic in the classic sense in mice, but that it also produced a high incidence of foetal death when given late in gestation, led us to initiate detailed studies on its foetal damaging effect in the perinatal period (I). The design of perinatal studies will be discussed in comparison with the design of teratological studies and in view of experiences

SUMMARY

In the present experimental studies the effect of salicylate resulting in both morphological damage and biochemical impairment of the mouse foetus have been demonstrated. Special interest has been devoted to looking for a relationship between the morphological derangement and biochemical action. Differences in foetal susceptibility to salicylate has been shown to be influenced by genetic as well as environmental factors.

The morhpological damage was foetal haemorrhages and death. A single i.m. injection of 500 mg/kg of sodium salicylate given to A/Jax mice on day 9 of gestation resulted in 20 per cent resorptions whereas after the same treatment on day 17 the incidence rose to 75 per cent. This observation became the introduction to studies of foetal damage induced late in pregnancy with special reference to day 17 of gestation. Haemorrhages located in the skin, liver and stomach could be observed as soon as 4 hours following treatment. Foetal death was first observed after 8 hours. The occurrence of foetal haemorrhages with subsequent foetal death suggests a close relation which could be corroborated by biochemical evaluation.

Biochemical impairment was demonstrated by changes in prothrombin time and glycogen concentration. Prothrombin time was prolonged in salicylate treated foetuses with haemorrhage but not in unaffected foetuses. This reduction of foetal prothrombin concentration is not necessarily the only underlying mechanism for the induced haemorrhage as coumarin treatment prolonged the prothrombin time without giving rise to any haemorrhage. Foetal liver glycogen was reduced by 4 hours following salicylate treatment in the A/Jax and CBA mice. This reduction was also observed after treatment with 150 mg/kg which did not induce visible foetal damage. No reduction in liver glycogen in relation to control animals could be found 24 hours following treatment. Heart glycogen was decreased only in A/Jax foetuses with haemorrhage. The observation of decreased prothrombin concentration and reduction of liver glycogen in the foetus suggests a close relation to the morphologically found liver haemorrhage and necrosis.

The number of foetal deaths after sodium salicylate treatment on day 17 decreased after two days pretreatment with a small dose of sodium salicylate (150 mg/kg) or a narcotic dose of pentobarbital. A strain difference between the A/Jax and CBA mice could be noted for induced foetal death but not for haemorrhage or reduction in liver glycogen. Distribution studies of ^{14}C-labelled salicylic acid with sodium salicylate as carrier between mother and foetus were made on days 14 and 17 of gestation. It was not possible to observe differences in distribution or elimination which could account for the observed strain difference or the effect of pretreatment. Further the method used cannot distinguish between the active and the detoxified substance.

Guidelines for perinatal study have recently been added to existing recommendations for drug tests. The present studies with sodium salicylate as a model substance can be used to discuss these recommendations and the question of dosage and acute versus chronic treatment. Three commonly used salicylate derivatives (sodium salicylate, acetylsalicylic acid and salicylsalicylic acid) were tested on day 17 of gestation based on the existing test recommendations. They all reduced foetal liver glycogen 4 hours after treatment and increased foetal death rate within 24 hours.

Clinical implications

"Extrapolation from experimental teratology to man is unwarranted unless supported by evidence in man" (50) Early reports on the effect of salicylic acid on foetal development contained warnings based first on a few cases of miscarriage and premature birth in humans and later supplemented with experiments in rabbits (12) Since then a few case reports concerning a possible relation between maternal ingestion of salicylate and foetal damage have been published. A sibship of four has been described in which the two eldest were born with phocomelia after maternal ingestion of aspirin (114) A case of congenital salicylate intoxication where the baby had a prolonged prothrombin time resistant to treatment with vitamin K has been published (43) A stillborn boy was delivered with cerebral haemorrhage after maternal ingestion of a toxic dose of salicylate though the cause of death probably was a tentorial tear (63) Neonatal ..ycaemia due to salicylate poisoning has been described in a 19 day old girl (106) Hemostatic defects have been demonstrated in newborns of mothers taking aspirin just prior to birth (15)

Studies made on maternal ingestion of drugs during pregnancy have shown a surprisingly high consumption (14 99) It is also well known that aspirin and related drugs are some of the most commonly used (33) Nine and one half per cent of blood samples taken from the umbilical vein at delivery have been shown to contain salicylate (10?) All of this indicated that its foetal damaging effect could not be very great (1 134) However a recent retrospective study of 833 malformed children in Wales showed a positive correlation between salicylate medications and anomalies (109) Additional studies are now in progress and should provide more exact information. This study will be most welcome. One would hope, however that it will consider salicylate s foetal damaging effect during late gestation as well.

27 Coldwell, B. B & Zawadzka Z. Effect of acute administration of acetylsalicylic acid on the prothrombin activity f bishydroxy-coumarin-treated rats. *Blood 32* 945 1968

28. McColl, J D Globus, M. & Robinson, S. Effect of some therapeutic agents on the developing rat fetus. *T lc Appl Pharmacol 7* 409 1965

29 McColl, J D Robinson, S & Globus, M. Effect of some therapeutic gents on the rabbit fetus. *T xic Appl Pharmacol 10* 244 1967

30 Conney A. H. Pharmacological implications of microsomal enzyme induction. *Ph rm col Rev 19* 317 1967

31 Cook, M J Fairweather F A & Hardwick, M. Further thoughts on teratogenic testing. *I* A. Bertelli & L. Donati (eds.) *Ter tolog* Excerpta Medica Foundation, Amsterdam 1969 p 34

32 Courtney K. D & Valerio, D A Teratology in the Macaca mulatta. *Ter tology 1* 163 1968.

33 Crotty J J The epidemiology of salicylate poisoning. *Cli T xicol, 1* 381 1968

34 Cushny A. R *Pharmacology d ther pe tic* J & A. Churchill Ltd., London 1947 13th ed p 695

35 Dallner G Studies on th structural and enzymic organization of the membranous elements of liver microsomes. *A ta Path Microbiol S d* Suppl. *166* 1963

36 Davey D G The study of the toxicity of potential drug-basic principles *I P oceed gs f th European society for th study f drug toxicity* 1965 ol. 6, p. 1

37 Dawes, G S., Mott, J C. & Shelley H J The importanc f cardiac glycogen for the maintenance of lif in foetal lambs and newborn animals during noxia. *J Physiol (London) 146* 516 1959

38 Dawson, A. B A not on the staining f the skeleton of cleared specimens with alizarin red S *Stain Tech 1* 123 1926.

39 Delphia, J M & Dutta S. The dose-dependent glycogen-depleting effect of sodium pentobarbital on the myocardium of the ra embryo during th sixteenth day of gestation. *Res Comm Chem P th Pharma ol 1* 355 1970.

40. Dixon, A S J Smith M J H Martin, B K., & Wood P H N *Salicylates.* J & A. Chur ch ll Ltd London 1963

41 Done A K Ontogenetic studies of salicylat intoxica ion *I* A. St. J Dixon, M J H. Smith, B K Martin & P H N Wood (eds.) *Salicylates* J & A Churchill Ltd., London 1963 p 260.

4_ Done A. K. Developmental pharmacology *Ch Pharmacol Ther 5* 432 1964

43 Earle R. Hazards to health. Congenital salicylate intoxication — Report of case *New E g J Med 265* 1003 1961

44 Earley P A. & Hayden, J Effec f acetylsalicylic acid on foetal rabbits *La t 1* 763 1961

45 Eriksson, M. & Larsson, K S. Premature birth induced in mice by salicylate. *Nature 220* 385 1968

46. Ernster L., Siekev tz P & Palade, G E Enzyme-structure relationships in the endoplasmic re iculum of ra liver A morphological and biochemical study *J Cell Biol 15* 541 1962.

47 E ans, G Packham, M. A Nishizawa, E E., Mustard, J F & Murphy E A. The effect of acetylsalicylic acid on platelet function *J E p Med 128* 877 1968

48 F ard, P & Jost, A Différenciation et harge en glycogène de l'hépatocyte d foetus de rat normal ou décapité *A h A at Micr Morph E p 55* 603 1966.

49 Food and Drug Administration (FDA) *Guidelines f prod ctio st die for safety evaluatio f drugs f huma use* USA 1966

50. Fraser F C Experimental teratogenesis in relation to congenital malformations in man. *I S nd international co feren on genit l malformations* The I ternational Medical Congress Ltd, New York 1963 p 277

51 Frick, P G Hemorrhagic diathesis with increased capillary fragility caused by salicylate therapy *Amer J M d Sci, 231* 402, 1956.

52 Gelli, M G Enhörning, G Hultman, E. & Bergstrom, J Glucose infusion in the pregnant rabbit and its effect on glycogen content and activ ty of foetal heart under anoxia *Act Paed at Scand 57* 1 1968

53 Goldman A S. & Yakovac W C. The enhancement of salicylate teratogenicity by maternal immobilization in the rat. *J Pharmacol Exp Ther 142* 351 1963

54 Goldman, A S & Yakovac, W C Salicylate intoxication and congenital anomalies. *Arch Environ H alth 8* 648, 1964

55 Goldman, A. S & Yakovac W C. Prevention of salicylate teratogenicity in immobilized rats by certain central nervous system depressants. *Proc Soc Exp Biol Med 115* 693 1964

56. Goldman, A. S. & Yakovac, W C. Teratogenic action in rats of reserpine alone nd in combination with salicylate and immobilization. *Proc Soc E p Biol Med 118* 857 1965

57 Gross, M. & Greenberg, L. A. *The salicylates. A critical bibliographic review* Hillhouse Press, New Haven 1948

REFERENCES

1 Adamsons, K. & Joelsson, I. The effects of pharmacologic agents upon the fetus and newborn. *Amer J Obstet Gynec* 96 437 1966.

2. Akiyama, N: Embryological studies on the congenital skeletal anomalies induced by acetyl salicylat (Aspirin) in rats. *Osaka City Med J* 16 645 1967

3 Alagille D Odievre, M Houllemare, L., Vlterbo G & Leroy D., Avitaminose K neonatale severe. *A k Franc Pediat* 25 31 1968.

4 Apgar V Drugs in pregnancy *JAMA* 190 840 1964

5 Baba, T., Nagahama, M., Akiyama, N & Miki, T Experimental production of malformations due to acetyl salicylate and phenyl salicylate in rats. *Osak C'ty M d J* 12 23 1966

6. Barilyak, I R. & Chebotar N A. Combined action of carbutamide and sodium salicylate on development of rat embryos. *B II E p Biol Med* 64 895 1967

7 Barnes, J M & Denz, F A.: Experimental methods used in determining chronic toxicity A critical review *Pharmacol R* 6 191 1954

8. Barnhart, M. I., Prothrombin synthesis An example f hepatic function. *J Hist hem Cytochem* 13 740, 1965

9 Barrow M V Quick, D T & Cunningham, R. W Salicylate hypoprothrombinemia in rheumatoid arthritis with liver disease. Report of tw cases. *A k Intern Med* 120 620 1967

10 Behrman, R. E. & Baratblia, F C. Protein binding of human fetal and maternal plasmas to salicylate *J Appl Physiol* 1 1.5 1967

11 Bernelli-Zazzera, A & Gaja, G Some aspects of glycogen metabolism following reversible or irreversible liv rschemia *E p Mole Path* 3 351 1964

12 Binz, C. Ueber Wirkung der Salicylsaure f die Gebarmu t *De I Kli W ch* XXX 983 1893

13 Bleyer W A & Breckenridge R T S les the detection of adv rse drug rea ns h newborn. II Th effects of prena newborn hemo ass *JAMA* 13

14 Bleyer W A., William, Y W., Lange W A. & Raisz, L. G Studies on th detection of adverse drug reactions in the newborn. I Fetal exposure to maternal medication. *JAMA* 213 2046, 1970.

15 Bloomfield, D K. Fetal deaths and malformations associated with the use of coumarin derivatives in pregnancy *Amer J Obstet Gyn c* 6 883 1970.

16. McBride, W G Thalidomide and congenital abnormalities. *Lancet* 2 1358 1961

17 Brown R. A. & West, G B. Effect of acetylsalicylic cid on foetal rats. *J Pharm Pharmacol* 16 563 1964

18 Bullock, G. R., Delaney V B., Sawyer B. C. & Slater T F Biochemical and structural changes in rat liver resulting from the parenteral administration of a large dose of sodium salicylate *Biochem Pharma ol*, 19 245 1970.

19 Burton, A. F Grenall, R. M. & Turnell, R. W: Corticosteroid metabolism and liver glycogen in fetal and newborn mice *Canad J Biochem* 48 178 1970.

20. Bywaters, E. G L. The history of salicylates. *I* A. St. J Dixon, M. J H. Smith, B. K. Martin P H. N Wood (eds.) *Salicylates* J & A. Churchill Ltd., London 1963 p. 3

1 Cad J F Hirsch, J & Martin, M., Placental barrier to coagulation factors: Its relevance to the coagulation defect t birth and to haemorrhage in the newborn. *Brit Med J* 2 281 1969

22. Cahen, R. Détermination de la toxicité des médicaments nouveaux. *Sem H p Paris*, 33 89 1957

23 Cahen, R. L. E aluation f the teratogenicity of drugs *Clin Pharmacol Ther* 5 480, 1964

4 Caruso, R. & Petrakis, N. L.: Studies of the coagulation and prothrombin time in the mouse embryo. *Th omb Diath Haemorrh* 16 752, 1966

5 Catz, C & Yaff S J: Barbiturate enhancement of bilirubin conjugation and excretion in young and adult animals. *P diat Res* 2 361 1968

Chambre yndicale nationale des fabricants de prod s pharmaceutiques *Des essais biologiques d hniq d méd aments* 1967

87 Mlempli, P H & Raihl, N C R. Effects of anoxia on energy-rich phosphates, glycogen la tat and pyruv t in the brai heart nd liver of the dev loping rat. *A M d E p Biol F* *46* 30(1968

88. Mahin T D & Lofberg, R T A simplified method of sample preparation for determination of tritium, carbon-14 or sulfur 35 in blood or tissue by liquid scintillation counting. *A al Bio-hem 16* 500 1966.

89 Mauer A. M., DeV ux, W & Lahey M E. Neonatal and maternal thrombocytopenic pu pura due to quinine. *Pediatrics 19* 84 1957

90. Mirkin, B. L. Effects of drugs on the fetus and neonat *Postgrad M d J 46* 91 1970.

91 Morf, E & Bretscher J Die anatomischen Hauptbef nde on 1061 perinatal erstorbenen Kindern. *G) ae ologia 161* 211 1966

92. Mork, D P S., Kessler W V & Shaw S. M. Placental transfer of pentobarbital in the rat *J Pharm S i, 6* 803 1970.

93 Mosher H. P Does nimal experimentation show similar changes in the ea of mother and fetus fter the ingestion of quinine by th mother? *Laryngoscope 48* 361 1938.

94 Mott, J C. The ability f young mammals to withstand total oxygen lack. *Brit Med Bull 17* 144 1961

95. Mountain, K. R Hirsh, J & Gallus, A. S. Neonatal coagulation defect due to anticonvulsant drug treatment in pregnancy *Lan t I* 265 1970.

96. Murphy M L. Teratogenic effects f tumour inhibiting chemicals in the foetal rat *I* G E. W Wolstenholme & C. M. O'Connor (eds.) *Ciba Fou dation Symposium C genital M l-formations* J & A Churchill Ltd London 1960 p 78.

97 The National Pharmaceutical Laboratory (SFL) *G id lines f th testing f drug animals for terat genicity* Sweden 1970.

98 Niederland, T R. Biochemical changes in liver kidney muscle myocardium, and th adrenals, f llowing the administration of various doses of salicylates. *I* A. St. J Dixon, M. J H Smith, B K Martin & P H. N Wood (eds.) *S licylat s.* J & A Churchill Ltd., London 1963 p 248.

99 Nora, J J Nora, A. H Sommerville, R. J Hill, R M. & M Namara, D G Maternal ex posure to potential teratogens. *JAMA 202* 1065 1967

100. Norén, I Specific assay of prothrombin. A method using freeze-dried reagent of intrinsic coagulation factors. *Sca d J Cli Lab I vest 25* 47 1970

101 Orrenius, S. & Thor H. F tty acid interaction w th the hydroxylating enzyme system of rat liver microsomes *E rop J Biochem 9* 415 1969

102 Palmisano P A & Cassady G Salicylat ex posure i the perinat *JAMA 209* 556 1969

103 Pantuck, E., Conney A. H & Kuntzman, R. Effect of phenobarbital on the metabolism of pentobarbital and meperidine in fetal rabbits and rats. *Biochem Pharmacol 17* 1441 1968

104 Pelz, L Iatrogene Vergiftungen beim jungen Säugling. *Pädiat Pra 7* 7 1968

105. Peters, V B., Kelly G W & Dembitzer H. M. Cytologic changes in fetal and neonatal hepati cells of th mouse *A N Y A ad S 111* 87 1963

106. Pickering, D Neonatal hypoglycaemia due to salicylate poisoning. *Proc Roy Soc Med 61* 1256 1968,

107 Picon, L. & Bouhnik J Action de la corticosur rénale sur la teneur d coeur en glycogène chez le foetus de rat et le ra nouveau-né. *C R Soc Biol 160* 288, 1966

108 Quick, A. J & Clesceri L Influence of acetylsalicylic acid and salicylamid on th coagulation of blood. *J Pharm al Exp Ther 128* 95 1960

109 Richards, I. D G Congenital malformations and environmental influences in pregnancy *Brit J Prev Soc M d 23* 218 1969

110 Rodriguez, S. U Leikin, S. L & Hiller M. C. Neonatal thrombocytopenia associated w th antepartum administration of thiazide drugs. *New E g J M d 270* 881 1964

111 Romney S L & Gabel, P V Maternal glucose loading in the management f fetal distress. *Amer J Obstet Gyne 96* 698, 1966.

112. Roueché, B *The incurable wound and f ther narratives f medical d tection.* Little Brown and Company Boston, Toronto 1957 p. 89

113 Samorajski, T Ordy J M. & Rolsten, C. Prenatal chlorpromazine effects on liver enzymes, glycogen, and ultrastructure in mice off spring *Amer J Path 47* 805 1965

114 Sayli B. S., Asmaz, A. & Yemisci, B. Consanguinity aspirin, and phocomelia. *La t I* 876 1966.

115 Schardein, J L. Blatz, A. T Woosley E. T & Kaump D H Reproduction studies on sodium meclofenamate in comparison to aspirin and phenylbutazone. *T xic Appl Pharmacol 15* 46, 1969

116 Schardein, J L., Woosley E. T Hamilton, L. E. & Kaump, D H Effects f aspirin and phenylbutazone on the rabbit blastocyst. *J Re prod Fertil 10* 129 1965

117 Schlüter C Embry toxische Dosis-Wirkungs-Beziehungen von Trypanblau bei Mäusen. V a-y S hmwd bc g A k Pharm 267 31 1970

118. Seifter S Dayton, S Novic B & Muntwyler E. The estimation f glycogen with the anthrone reagent. A k Biochem 25 191 1950.

119 Shelley H. J: Glycogen reserves and their changes t birth and in anoxia. Brit M d B ll 17 137 1961

120 Shelley H. J Carbohydrate reserves in the newborn infant. Brit M d J 1 273 1964

1 1 Shelley H. J The metabolic response f the fetus to hypoxia. J Obstet Gyne Brit Comm 76 1 1969

122. Smith, M. J H & Smith, P K. The salicylates. John Wiley and Sons, Inc., New York 1966

1.3 Somers, G F The foetal toxicity of thalidomide. I P oc edings of th European Society for the Study f Drug T xicity Excerpta Medica Foundation, Amsterdam 1963 p. 49

124 Sproull, D H. The glycogenolytic action of sodium salicylate. Brit J Pharmacol, 9 121 1954

125 Sturman, J A., Dawkins, P D McArthur N. & Smith, M J H. The distribution of salicylat in mouse tissues after intraperitoneal injection. J Pharm Pharmacol 20 58, 1968.

126. Sturman, J A. & Smith, M. J H. The binding of salicylate to plasma proteins in different species. J Pharm Pharmacol, 19 621 1967

127 Takacs, E. & Warkany J Experimental production of congenital cardiovascular malformations in rats by salicylate poisoning. Teratology 1 109 1968.

128. Takeda, Y Gabel, P V & Romney S L. Effects f maternal glucose loading upon induced fetal distress. Amer J Obstet Gynec 96 872, 1966.

129 Trasler D G Aspirin-induced cleft lip and other malformations in mice La t 1 606, 1965.

130 Tuchmann-Duplessis, H. Design and interpretation of teratogenic tests. I J M Robson, F Sullivan & R. L. Smith (eds) Biological Council Symposium Embry pathic ctivity f drugs. J & A. Churchill Ltd London 1965 p. 56

131 Uhlenbruck, K. & Freier G., Zur Frage der Auslösung foetotoxischer Effekt durch M gnesiumacetylsalicylat. Arz eim ttelf rsch g 18 195 1968

132. Vogel, M Leberbefunde bei Neugeborenenasphyxie. Msch K nderheilk 115 346 1967

133 Waddell, W J & Marlowe, C.: The distribution of teratogenic gents in pregnant mice. Teratology 2 273 1969

134 Warkany J Discussion. I G E. W W lstenholme & C. M. O'Connor (eds.) Ciba Fou dation Symposium n Co genital Malformations J & A. Ch rchill Ltd., London 1960, p. 135.

135 W rkany J & Takacs, E. Experimental production of congenital malformations in rats by salicylat poisoning. Amer J Path 35 315 1959

136 Weinberg, M. S., Goldhamer R. E. & Carson, S Acute oral toxicity of various drugs in new born rats fter treatment of the dam during gestation. T xic Appl Pharmacol 9 234 1966.

137 W j ja, L., Snijder J A. M. & Nieweg, H O Acetylsalicylic acid as a cause of pancytopenia from bone-marrow damage. Lan t 2 768, 1966.

138. Wilson, J G Terat logical and reprod cth studies in non-huma primates. I H. Nishimura & J R. Miller (eds.) Methods f teratological st die perimental animals and m Igaku Shoin Ltd., Tokyo 1969 p 16.

139 World Health Organization (WHO) Principles for the testing of drugs for teratogenicity Re port of WHO scientific group. WHO Tech R p Ser 364 1967

140 Wright, H. N Chronic toxicity studies f analgesic and antipyretic drugs and congeners. T xic Appl Pharma l 11 280 1967

141 Yaffe, S J Fetal and neonatal toxicity of drugs. C nad Med Ass J 98 301 1968.

142 Y ff S J Krasner J & Catz, C. S. Part III Genetic ariations that modify drug response. Variations in detoxication enzymes during mammalian development. A N Y A ad Sci 151 887 1968

143. Zilliacus, H., Ottelin, A M Karinlemi V Mattsson, T & Teramo K Blood lotting and fibrinolysis in human foetuses I Abst cts Xth Co g ess f th I tern tio l Society f Hematology Stockholm 1964 p G-92.

117 Schlüter G Embry toxische Dosis-Wirkungs-Beziehungen von Trypanblau bei M usen. *Naunyn S hmiedeberg A ch Pharm 267* 31 1970

118 Seifter S Dayton, S Novic B. & M ntwyler E. The estimation f glycogen with th anthrone reagent. *A ch Biochem, 5* 191 1950

119 Shelley H. J Glycogen reserves and their changes at birth and in anoxia. *Brit M d B ll 17* 137 1961

120 Shelley H. J Carbohydrate reserves in the newborn infant. *Brit M d J 1* 273 1964

121 Shelley H J The metabolic response of the fetus t hypoxia. *J Ob tet Gyna Brit Comm 76* 1 1969

122 Smith, M. J H. & Smith, P K. The salicylates. John Wiley and Sons, Inc., New York 1966.

123 Somers, G. F Th foetal toxicity of thalidomide *I P oce d gs f the Eu pe Society for the Study f Drug T xcity* Excerpta Medica Foundation, Amsterdam 1963 p 49

124 Sproull D H. The glycogenolytic action of sodium salicylat *Brit J Pharmac l 9* 1 1 1954

125 Sturman, J A., Dawkins. P D McArthur N & Smith, M. J H Th distribution of salicylate in mouse tissues after intraperitoneal injection. *J Pharm Pharmacol 20* 58 1968.

126. Sturman J A. & Smith M. J H. The binding of salicylate to plasma proteins in different species. *J Pharm Pharmacol, 19* 621 1967

127 Takacs, E. & Warkany J Experimental production f congenital cardiovascular malformations in rats by salicylate poisoning. *Ter tology 1* 109 1968.

128. Takeda, Y Gabel, P V & Romney S. L. Effects of maternal glucose loading upon induced fetal distress. *Amer J Obstet Gy 96* 872, 1966

129 Trasler D G: Aspirin-induced cleft lip and other malformations in mice *Lan et 1* 606, 1965

130 Tuchmann-Duplessis, H Design and interpretation of teratogenic tests. *In* J M. Robson, F Sullivan & R. L. Smith (eds.) *Biologic l Co cil Symposi m Embry pathi ctiv ty f drug* J & A. Churchill Ltd London 1965 p 56.

131 Uhlenbroock, K. & F eler G Zu Frage der Auslösung foetotoxischer Effekt durch Magnesiumacetylosalicylat. *A n im tt lfo sch g 18* 195 1968

132 Vogel, M Leberbefunde bei Neugeborenenasphyxie *Msch Kinderh ill 115* 346 1967

133 Waddell W J & Marlowe C. The distribution f teratogenic agents in pregnant mice. *Teratology 2* 73 1969

134 Warkany J Discussion. *I* G E. W Wolstenholme & C. M. O'Connor (eds.): *C ba F nda tio Symposium n C genital Malformations.* J & A. Churchill Ltd., London 1960 p. 135.

135 W rkany J & Takacs, E. Experimental production of congenital malformations in rats by salicylate poisoning *Amer J Path 35* 315 1959

136 Weinberg M S Goldhamer R. E. & Carson, S Acute ral toxicity f various drugs in newborn rats after treatment of the dam during gestation. *Toxic Appl Ph rma ol 9* 234 1966.

137 Wijnja L., Snijder J A. M. & Nieweg, H. O Acetylsalicylic acid as a cause f pancytopenia from bone-marrow damage. *Lanc t 2* 768, 1966

138. Wilson, J G Teratological and reproductiv studies in non-human primates. *I* H. Nishimura & J R. Miller (eds.) *Methods for teratological st die experimental anim ls and m* Igaku Shoin Ltd., Tokyo 1969 p. 16.

139 World Health Organization (WHO): Principles for the testing of drugs for teratogenicity Report of a WHO scientific group. *WHO Tech Rep Ser 364* 1967

140. Wright, H N Chronic toxicity studies of analgesic and antipyretic drugs and congeners. *Toxi Appl Pharma ol 11* 280 1967

141 Yaffe, S J Fetal and neonatal toxicity of drugs. *C nad M d Ass J 98* 301 1968

142. Yaffe, S. J Krasner J & Catz, C. S Part III Genetic variations that modify drug response. Variations in detoxication enzymes during mammalian dev lopment. *Ann N Y Acad Sci 151* 887 1968.

143 Zilliacus, H., Ottelin, A. M., Karinlemi, V Mattsson, T & Teramo, K. Blood clotting and fibrinolysis in human foetuses. *I Abst cts Xth C g ss f the I tern tional Society f Hematol gy* Stockholm 1964 p. G:92.

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 212 1971

URINARY EXCRETION OF VANILMANDELIC ACID OF CHILDREN IN NORMAL AND CERTAIN PATHOLOGICAL CONDITIONS

BY ALPO HAKULINEN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

URINARY EXCRETION OF VANILMANDELIC ACID OF CHILDREN IN NORMAL AND CERTAIN PATHOLOGICAL CONDITIONS

ACTA PAEDIATRICA SCANDINAVICA
SUPPLEMENT 212, 1971

From the Department of Pharmacology (Head: Professor Atmo Pekkarinen, M.D.)
and the Children's Hospital of the University of Turku,
(Head: Professor Tuomas Peltonen M.D.), Turku, Finland

URINARY EXCRETION OF VANILMANDELIC ACID OF CHILDREN IN NORMAL AND CERTAIN PATHOLOGICAL CONDITIONS

BY

ALPO HAKULINEN

The micromodification of the determination
of vanilmandelic acid in the urine (by Atmo Pekkarinen & Alpo Hakulinen)
used in the present work is described
in the Appendix

KUOPIO 1971

Printed in Finland

Kirjapaino Oy Savo offsetpaino Kuopio 1971

To Inken and my sons

CONTENTS

INTRODUCTION 9
REVIEW OF THE LITERATURE 11
Adrenaline and noradrenaline metabolism and vanilmandelic acid 11
Adrenaline and noradrenaline metabolism during the fetal period 12
Urinary excretion of vanilmandelic acid in normal conditions 13
Effect of age 13
Neonatal period 13
Older infants and children 16
Adults 16
Diurnal rhythm 17
Sex difference 17
Effect of psychic tension and physical exercise 17
Urinary excretion of vanilmandelic acid in pathological conditions 18
Catecholamine-secreting tumors 18
Surgical operations 19
Burns 20
Traumatic shock 20
Cardiovascular diseases 20
Respiratory diseases 21
Hepatic diseases 21
Renal diseases 21
Some hormonal diseases 21
Disorders of the autonomic nervous system 21
Neurological and mental diseases 22
Other diseases 22
Effect of drugs or diet 23
Stability of vanilmandelic acid in the urine 23
PURPOSE OF STUDY 25
MATERIAL AND METHODS 26
Children in normal conditions 26
Newborn infants 26
Children between 1 week and 15 years 26
Children with certain pathological conditions 27
Technique of urine collection 29
Determination of urinary vanilmandelic acid 29
Statistical treatment 29
RESULTS 30
Urinary excretion of vanilmandelic acid in normal conditions 30
Age groups between birth and 15 years 30
Annual increment 34
Correlation to age, body weight and urine volume 35
Sex difference 35
Diurnal rhythm 35

Other normal conditions studied 37
Urine volume 37
Urinary excretion of vanilmandelic acid in certain pathological conditions 37
Observed increased excretion 37
Neuroblastoma and pheochromocytoma 37
Surgical operations 39
Congenital heart disease with or without heart failure 40
Febrile infections 40
Acute bronchial asthma 40
Exchange transfusion in hemolytic disease of newborn 41
Observed decreased excretion 41
Observed normal excretion 41
DISCUSSION 44
Urinary excretion of vanilmandelic acid in normal conditions 44
Newborn infants 44
Children between 1 week and 15 years 45
Urinary excretion of vanilmandelic acid in certain pathological conditions 48
Increased excretion 48
Decreased excretion 52
Normal excretion 53
SUMMARY 54
ACKNOWLEDGEMENTS 57
REFERENCES 58

APPENDIX 1

ABBREVIATIONS

A	Adrenaline
COMT	Catechol o-methyltransferase
DHMA	3 4 Dihydroxymandelic acid
DHPG	3 4 Dihydroxyphenylglycol
5 HIAA	5 Hydroxyindoleacetic acid
HVA	Homovanillic acid
MA	Methyladrenaline
MAO	Monoamino oxidase
MHPG	3 Methoxy 4 hydroxyphenylglycol
MNA	Methylnoradrenaline
NA	Noradrenaline
VA	Vanillic acid
VMA	Vanilmandelic acid

INTRODUCTION

The discovery that vanillmandelic acid (VMA) is the main metabolite of adrenaline (A) and noradrenaline (NA) (7) led soon to the clarification of the major pathways of metabolism of these hormones (page 11). The methods for the urinary determination of the major metabolites of and NA were available shortly thereafter also for use in clinical diagnosis. The determination of A and NA excretions in the urine is still, however, the most reliable criterion of the activities of the sympathetic nervous system and the adrenal glands (68). The usefulness of excretion studies for this purpose is well supported also by the investigations of Pekkarinen and his working group (57, 111, 158, 194, 196, 198, 207, 222).

The possibility of determining the metabolites of A and NA has, however, opened new opportunities for the study of both the physiological significance of these hormones and their normal and pathological secretion and metabolism. Examination of these metabolites in the urine is usually more practical owing to their stability and great quantities. This is true of VMA, which is excreted in the urine in about 70 times as large amounts as A and NA together (292).

The excretion of VMA in the urine has been extensively studied in adults in the normal state (page 16) and in many pathological conditions. Thus we know that the excretion of VMA is increased in cases of tumor of the adrenal medulla (6), and in neuroblastoma (257) in which its determination is of great diagnostic significance. VMA excretion is also increased in patients with burns (6) as well as in connection with major surgical operations (195, 244, 299), indicating that certain stress factors may increase the excretion. Concerning the correlation between urinary VMA and A and NA excretion in man there is, however, very little information in the literature. Jacobs *et al.* (128) did not find such correlation in the 24 hour outputs of 91 laboratory workers, whereas in 16 confirmed cases and 19 suspected cases of pheochromocytoma a correlation between urinary VMA and combined A and NA concentrations was apparent ($r = 0.85$, $p < 0.001$).

There are also several investigations on normal VMA excretion in children (Table) but the series studied have, with a few exceptions, been small. On the other hand, very few investigations have been published on the neonatal period and on disease conditions in children. We know that liver and kidney functions in infants and particularly in newborn infants are still immature, and this may influence the enzymatic degradation of A and NA and the excretion of their metabolites. On the other hand, the early functional activity of the sympathetic nervous system is indicated, e.g., by an elevation of both A and NA excretion in response to feet down tilting in children 1—7 days old (104) and by a rise in blood pressure in response to orthostatic stress in newborn on the average from the fourth day onwards (110, 112). However, functional imbalances of the vegetative nervous system are not rare in children in any age group (21, 21) and also in pediatric practice symptoms of high sympathetic and adrenomedullary activity are, in the present author's opinion, not uncommon in children. The reactions in the sympathetic and adrenomedullary system in children may differ from those in adults and differences can be expected also in the excretion of A and NA metabolites, e.g., VMA excretion.

These aspects of the study and the special need of normal data on healthy children during progressive development in childhood directed the present author to study normal child series in order to clarify the urinary VMA excretion values in the different age groups of Finnish children. The results of part of these studies have been published elsewhere (108, 109). Another object was to screen

the urinary VMA excretion in various pathological conditions in childhood and to compare findings with the normal series. The main attention was directed to those disease groups that are of special interest for the topic of sympathetic and adrenomedullary function.

As a study carried out both in the D partment of Pharmacology and in the Childre Hospital of the University of Turku t present investigation seeks also to make contribution to research work in clin pharmacolog

REVIEW OF THE LITERATURE

ADRENALINE AND NORADRENALINE METABOLISM AND VANILMANDELIC ACID

The metabolism of adrenaline (A) and noradrenaline (NA) may initially begin with o-methylation by catechol-o-methyltransferase (COMT) into methyladrenaline (MA) and methylnoradrenaline (MNA) (12 15) Part of these methylated compounds are excreted in the urine (15) and a part are further deaminated by monoamino-oxidase (MAO) into 3 methoxy-4 hydroxymandelic acid or vanilmandelic acid (VMA) (7) or are transformed by reduction to 3-methoxy-4 hydroxyphenylglycol (MHPG) (15) and excreted in the urine Alternatively A and NA can be deaminated in a primary process, resulting in 3 4-dihydroxymandelic acid (DHMA) (147) a part of which is excreted in the urine but a large part is o-methylated into VMA (Fig 1) VMA is mainly excreted unchanged in the urine but only a very small fraction is oxidized further into vanillic acid (VA) (63 250 293) A few other smaller metabolites of A and NA have been demonstrated

Among the metabolites of endogenous adrenaline and noradrenaline VMA predominates being about 70 times the amount of the free A and NA excreted into the urine and about 10 times the amount of the total MA+MNA in the urine (26, 292)

Following an infusion of radioactive A or NA into man about 4 per cent of the total dose is excreted into the urine as free hormone, slightly more than a third as VMA, and about the same amount as combined MA+MNA (93 147 156 166)

The part of radioactive NA injected into the circulation or the endogenous NA released from the noradrenergic neurones is rapidly taken up by the tissues containing the noradrenergic innervation (15 323) and is stored for the greater part as chemically unchanged

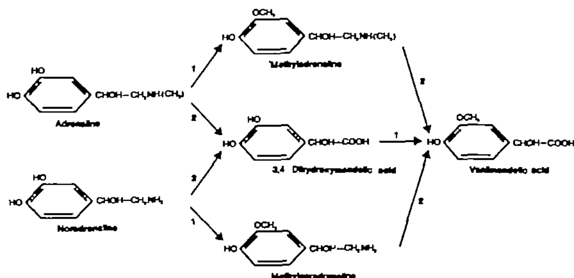


Fig 1 O-methylation and deamination of adrenaline and noradrenaline into vanilmandelic acid 1) catechol-o-methyltransferase 2) monoamine oxidase (in schematic presentation)

NA in the noradrenergic neurones or granules (223) This uptake or re uptake mechanism is the most important factor in inactivation of exogenous and endogenous NA and A in the organism (9 10) and is of greater importance as an inactivation mechanism than their enzymic degradation by methyl transferases or monoamino-oxidases. The binding into a noradrenergic neurone is a relatively more important mechanism for this inactivation of circulating NA and enzymatic o methylation again is more important for A (9 10)

A small part of active NA is released *spontaneously from the storage form of NA* but more is released after sympathetic nerve impulses (115 248) A small fraction of the released active noradrenaline reacts with the adjacent receptors and has thus a physio logical function The remainder of NA is to a great extent re bound to the noradrenergic nerve endings or partly inactivated rapidly by o methylation, or is washed off by the blood stream. Little if any is deaminated (9 115)

Kopin (156) studied the relative importance of o methylation and deamination in A metab olism in man by the double isotope method The metabolites were determined in the urine 40 hours after simultaneou administration of H A and C[14] MA. About 70 per cent of the administered A was first o methylated to MA and 20 per cent was deaminated to DHMA About a half of the MA was excreted unchanged or as sulphate or glucuronide conjugate and a half was deaminated and *oxidized to VMA or reduced to MHPG*

The relative importance of MAO and COMT in the enzymic degradation of A and NA depends upon the extra and intra neuronal amounts of these transmitters in the sympathetic and adrenomedullary systems and upon the amou it of noradrenergic innervation of tissues and or the animal species (10)

The action of COMT is directed mainly upon extraneu onal NA in the tissues or in the circulating bl ood (157 159 160 189) whereas the degradat on of storage NA is mainly effected by MAO *in situ* (159) The release of this deaminated material i probably independent of nerve impulses and when released it may be ex reted unchanged in the urine (DHMA and DHPG i.e 3 4 di hydroxyphenylglycol) or DHMA is o methylated further nd i transformed to VMA (158) The VMA thus formed i probably the main source of the VMA i the urine and represents noradrenaline that metabolized before having had any physic logical action (158)

In fact it has been suggested that und *normal conditions the amount of VMA i* the urine should be regarded as an index o the synthesis of catecholamines rather tha that of the activity of the noradrenerg nervous system (331)

ADRENALINE AND NORADRENALINE METABOLISM DURING THE FETAL PERIOD

The heart kidneys and lungs of the huma fetus had approximately the same amoun of A and NA as those of the adult o other species, whereas the contents of thei hormones were much lower in the fetal tha in the adult brain (103) The content of in the brains of newborn animals was th higher the more developed the species wa at birth (139)

Both A and NA are present in huma amniotic fluid in small amounts (42 161 The A and NA contents of the amnioti fluid in toxemic patients did not markedl differ from that in the controls (42)

C[14] A and C[14] NA injected into the cir culation of the mother was recovered i considerable amounts from the placental blood flow to the fetus, whereas only traces wer *found in the blood returning to the mothe* (259) Schaepdryver [cited by Gitlow (78) demonstrated in a pregnant woman wit pheochromocytoma that catecholamines pene trate the placental barrier and that the pla centa is capable of changing these hormone to VMA After C[14] NA injection into th *maternal* spiral artery MNA DHMA, VM and VA were detected in the fetal perfusat together with unchanged NA, which indicate that both MAO and COMT were involved in its inactivation (186)

Castrén *et al.*(38) studied the metabolism of i administered H[3] NA in the human feto and placenta A large amount of H[3] MNA was demonstrated in the liver of 5 month old fetuses, whereas H[3] DHMA and H VMA were present in small amounts only This point to the relative significance of

COMT in the metabolism of NA under these conditions. On the same basis, the brain of fetuses of the same age showed slight COMT activity but MAO activity was not clearly demonstrable. Placentas examined in the 3rd to 10th months of pregnancy revealed both COMT and MAO, and with maturing of the placenta there was an increase in the metabolism of H NA. Maternal diabetes and placental degeneration had no effect on the amount of NA metabolism, but in the degenerated placenta the metabolism appeared to occur to a relatively greater extent through the action of COMT.

URINARY EXCRETION OF VANILMANDELIC ACID IN NORMAL CONDITIONS

Effect of age

Neonatal period (with attention also to A and NA excretion)

VMA is excreted in the urine from the first day of life (23, 108, 191, 292, 33; Table 1). The VMA excretion increases daily and already during the first week attains about the same level expressed in µg/kg at which it remains during the later years of childhood (103, 33).

When the VMA excretion is expressed in µg/mg creatinine the postnatal excretions are highest and the excretion decreases with increasing age (84, 89, 292). The VMA content in the urine (VMA in µg/ml) in fullterm infants is also higher on the first day than on the following days (292).

In the premature newborn the VMA excretion in absolute terms is lower in the first week than in the fullterm newborn, but when calculated per kg body weight it correspond to that of the latter (23, 108). However, in a study by Nicolopoulos *et al.* (191) the excretion of VMA in fullterm and premature infants was on the first day 4—5 times that observed by the present writer (108) on the 15th day of life the VMA excretion of the prematures was extremely high, 2506 µg/24 hrs, whereas that of fullterm infants was even slightly lower than on the first day (191).

Table 1. *Urinary UMA excretion of fullterm infants in the neonatal period as reported by various authors (I=UMA µg/24 hrs and µg/kg/24 hrs. II=UMA µg/mg creatinine)*

I Authors	Age	No. of cases	VMA excretion µg/24 h	VMA excretion µg/kg/24 h
Zeisel, 1961 (332)	1st day	5	60	18
	3rd	5	150	50
	6th—8th days	8	270	80
	2nd—4th weeks	13	170—190	50—54
Beckm & O'Brien, 1964 (23)	1st day	4		47
	3rd	5		71
	5th	5		148
Hakulinen, 1966 (108)	1st day	30		35
	2nd	29		54
	4th	23		75
	5th	16		84
Nicolopoulos *et al.*, 1968 (191)	1st day	11	606±429	
	15th	9	471±196	

II Authors	Age	No. of cases	VMA excretion, µg/mg creatinine Mean	Range
Studnitz, 1960 (292)	1st day	6	10.6	5.0—18.3
	3rd	6	5.4	5.0— 7.3
Gjessing, 1966 (89)	2nd week	6	6.2	4.0— 9.0
Lees, 1966 (169)	30±15 days	13	10.1± 4.7	
Nicolopoulos *et al.*, 1968 (191)	1st day	11	15.8±13.7	
	15th	9	13.6± 5.8	

NA in the noradrenergic neurones or granules (223) This uptake or re-uptake mechanism is the most important factor in inactivation of exogenous and endogenous NA and A in the organism (9 10) and is of greater importance as an inactivation mechanism than their enzymic degradation by methyl transferases or monoamino oxidases The binding into a noradrenergic neurone is a relatively more important mechanism for this inactivation of circulating NA, and enzymatic o methylation again is more important for A (9 10)

A small part of active NA is released spontaneously from the storage form of NA, but more is released after sympathetic nerve impulses (115 248) A small fraction of the released active noradrenaline reacts with the adjacent receptors and has thus a physiological function The remainder of NA is to a great extent re-bound to the noradrenergic nerve endings or partly inactivated rapidly by o-methylation, or is washed off by the blood stream. Little if any is deaminated (9 115)

Kopin (156) studied the relative importance of o-methylation and deamination in A metabolism in man by the double isotope method The metabolites were determined in the urine 40 hours after simultaneous administration of H A and C^{14} MA About 70 per cent of the administered A was first o-methylated to MA and 90 per cent was deaminated to DHMA. About a half of the MA was excreted unchanged or as sulphate or glucuronide conjugate and a half was deaminated and oxidized to VMA or reduced to MHPG

The relative importance of MAO and COMT in the enzymic degradation of A and NA depends upon the extra and intra neuronal amounts of these transmitters in the sympathetic and adrenomedullary systems and upon the amount of noradrenergic innervation of tissues and on the animal species (10)

The action of COMT is directed mainly upon extraneuronal NA in the tissues or in the circulating blood (157 159 160 189) whereas the degradation of storage NA is mainly effected by MAO in situ (159). The release of this deaminated material is probably independent of nerve impulses, and when released it may be excreted unchanged in the urine (DHMA and DHPG i e 3 4-dihydroxyphenylglycol) or DHMA is o methylated further and is transformed to VMA (159). The VMA thus formed is probably the main source of the VMA in the urine and represents noradrenaline that is metabolized before having had any physiological action (158).

In fact it has been suggested that under normal conditions the amount of VMA in the urine should be regarded as an index of the synthesis of catecholamines rather than that of the activity of the noradrenergic nervous system (331)

ADRENALINE AND NORADRENALINE METABOLISM DURING THE FETAL PERIOD

The heart, kidneys and lungs of the human fetus had approximately the same amount of A and NA as those of the adult of other species, whereas the contents of these hormones were much lower in the fetal than in the adult brain (103). The content of A in the brains of newborn animal was the higher the more developed the species was at birth (139)

Both A and NA are present in human amniotic fluid in small amount (42 161) The A and NA contents of the amniotic fluid in toxemic patients did not markedly differ from that in the controls (42)

C^{14} A and C^{14} NA injected into the circulation of the mother was recovered in considerable amounts from the placental blood flow to the fetus, whereas only traces were found in the blood returning to the mother (259) Schaepdryver [cited by Gitlow (78)] demonstrated in a pregnant woman with pheochromocytoma that catecholamines penetrate the placental barrier and that the placenta is capable of changing these hormones to VMA. After C^{14} NA injection into the maternal spiral artery MNA, DHMA, VMA and VA were detected in the fetal perfusate together with unchanged NA which indicated that both MAO and COMT were involved in its inactivation (186)

Castren et al (38) studied the metabolism of i.v. administered H NA in the human fetus and placenta. A large amount of H^3 MNA was demonstrated in the liver of 3 month old fetuses, whereas H^3 DHMA and H VMA were present in small amounts only Thus points to the relative significance of

Table 2 *(cont.)*

II Authors	Ag 0—12 months				Age 1—10 years				Age over 10 years			
	Months	No. of cases	VMA excretion, µg/mg creatinine Mean	Range	Years	N of cases	VMA excretion, µg/mg creatinine Mean	Range	Years	No. f cases	VMA excretion, µg/mg creatinine Mean	Range
Studnitz, 1960 (292)					4—10		5 9±0.44	3.0—8 0				
Gitlow *et al* 1965 (84)	<12	)	7 0	1 4—15	1<2 2<5 5<10	)	4.6 4.3 2.5	1 3—8 1.5—7.5 0.5—5 5	12<15 >15	**)	1.9 1.3	0.5—3.3 0 2—2.8
Gjessing 1968 (89)		)			<3 3—12	)		12—2 3—1.5				
III Author	**Age 0—12 months**				**Age 1—18 years**				**Age over 15 years**			
	Months	No. of cases	VMA excretion, µg/m²/24 h Mean	Range	Years	N of cases	VMA excretion, µg/m²/24 h Mean	Range	Years	No. f cases	VMA excretion, µg/m²/24 h Mean	Range
Voorhess, 1967 (311)	0—12	19	2021	893—5211	1—5 6—15	15 13	2001 2133	1033—3180 1750—2846	>15	13	1931	1171—2576
IV Author							VMA excretion, µg/liter Mean	Range				
Young *et al.*, 1963 (340)					<2 2—14	)	2.3±2.4 4.3±2.3	0.1—8.6 0—10.2				

) Values are taken from the mean regression line of the daily VMA excretion f 96 subjects (healthy children and active hospitalized children with non specific minor ailments)

**) Series of 106 normal subjects from 3 weeks to 18 years f age

***) 90 healthy children from 5 weeks to 12 years of age and 40 sick hospitalized children from 4 weeks to 3 years of age

**) 65 children from 1 week to 14 years f age with non-specific minor ailments

The MA+MNA/VMA ratios on the first and third days of life were 72 5 ± 11 and 14 2 ± 19 in premature infants and 5 4 ± 3 ? and 4 5 ± 3 in fullterm newborn infant (27) The difference between the ratios in premature and fullterm infants was significant The ratio values in both groups differed also from those in the adult group this difference was ascribed by the authors to the absence of MAO in newborn infant which results in increased o-methylation However Greenberg & Gardner (100) were of the opinion that A administered to newborn infant is metabolized in a manner similar to that in adults.

A rise of 5 9 in the VMA excretion was seen in 16 children 4—9 days old age when the environmental temperature was lowered from 29 4 to 25 9°C (.58)

A and NA in the urine of the newborn 0 6 —0 8 μg/ 4 hrs of NA and 0 1—0 4 μg/ 4 hr of A are excreted (59 101 333) While the A excretion per kg of body weight by the newborn was nearly the same as that by children 1 5—6 years of age the excretion of NA was only one third of that in the latter (59 138) During the first three days of life the highest mean excretion of A was seen on the first day whereas the NA excretion gradually increased during this period (59) In premature infant the A excretion on the 1st and 15th days of life approximately corresponded to those of fullterm infants, whereas the NA excretion on both days was significantly lower than in the fullterm infants whether calculated per 24 hours or per kilogram per 24 hours (190)

Feet down tilting of children aged 1—7 days raised the NA excretion to 2.5 fold and the A excretion to 2 4 fold (104) in children 4—36 days of age the value was 3 7 and 2 8 fold respectively (116) Greenberg *et al* (104) demonstrated also a selective adrenaline response to insulin induced hypoglycemia

Older infants and children

The daily excretion of VMA per unit of body weight is highest in early infancy (43 191 311 332 Table 2) after which there is a slight gradual decrease On the other hand the absolute excretion of VMA increases with age throughout childhood and there is a good linear correlation between VMA excretion and the age (174 181 304) and the weight of the child (181)

When VMA excretion is expressed on the basis of creatinine output decreasing excretion readings are obtained with increasing age and the adult level is attained at the age of 15 years (81) In relation to body surface area the mean VMA excretion was nearly similar in all the age groups (311) however these excretions showed a fairly wide dispersion.

Adult

In the quantitative determinations of VMA the mean urinary excretions in adults vary owing to differences in technique in the range 1 2—7.5 mg/24 hrs the mean of all mean values given in the literature being 3 7 mg/ 4 hrs (6 5 59 65 70 76 158 163 176 184 197 203 205 208 209 13 221 240 243 47 55 26 270 292 301 309 328 329) When expressed on the basis of the VMA/creatinine ratio the range values for VMA excretion of adults have been 0 8—7.5 mean being 2 7 μg/mg creatinine (6, 76 80 148 164 184 213 292 296 297 301 309 324 325)

Using the present method, Pekkarinen and his co-workers determined the urinary VMA excretion in some conditions. In soldiers (n=50) during normal military service it was 5 2 ± 0.38 (S E.M) mg/24 hrs (203) in hospitalized psychiatric male patients (n = 18) 4.5 ± 0.32 mg/24 hrs (209), in hospitalized cerebrovascular patients (n=29 male and female) 4 5 ± 0 19 mg/24 hrs (208) and in surgical patients (n=67) on the preoperative day 3 8 ± 0 1 mg/24 hrs (195 205)

The mean VMA content of urine has been found to be 5 9 (range 1 4—10.5) μg/ml (292) and 4 4 (range 1 1—9 1) μg/ml (213)

The daily excretion of VMA is fairly constant in the same individual but there is considerable variation between individuals (152 210 309).

The intrapair variance of VMA excretion in monozygotic twins was smaller than in dizygotic twins and it was especially small among those monozygotic pairs who had been living together for more than 28 years (164) Race and the nutritional state influence the absolute VMA excretion values. So

for instance ndigent and emaciated hind s excreted less VMA than well nourished indi viduals (113)

Neither the premenstrual phase nor menstrua tion caused a rise in VMA excretion (88) In a series of 113 women with normal pregnancy the VMA excretion during the last t mester was 4 1 ± 0 15 (S E.M) mg/24 hrs, or th same as in the control series (197) Neither were any changes observed in another study n the excretion at the end of pregnancy (41)

Diurnal rhythm

The excretion of VMA of children has been found to be higher during the day than at night (103 174) A imilar da ly *rhythm has been observed in adult* 185 195 213 267 292 301 321) The VMA excretion n adults was on the er g 175 ± 68 µg/hr in daytime and 85 ± 31 µg/hr during sleep (267) Values up to 214 ± 103 and 124 ± 54 µg/hr espectively ha also been reported (27) The differenc between nocturnal nd daytim excretion wa mostly dependent on the st te of wakefulness, while the effect of standing positio wa hardly noticeabl (182) No sign ficant day/ night variation in the VMA ex retion was however observed in Korean ad lt (15)

T utz *l al.* (303) distributed the person into three groups according to their VMA excretions during 24 hrs The first group had high morni g and a relatively high ight excretion, which was typical for sym pathicotonic indiv duals th second had low morning and night excretions, which wa typical of vagotonic individuals, nd the third, a non-characteristic group omprised most other persons

Sex difference

N d fference in the 24 hour VMA ex cretion was de ionstrable between boy and gi l 1—11 9 years of age but in those ged 12—15 9 years ther w notabl difference (174) The investigators considered however the pos bility that the rine samples f om the latter group of girl wer not omplete 24 hour excretion in all of the ases. No ma ked sex d fferenc w seen by Terslev (304) in the excretion of VMA in 60 ch ldren (2 months to 14 years) nor b Matsaniotis *et al* (181) in 30 ch ldren (to 1⊥5 years)

Weise *et al* (321) found in adults that the total VMA excreted 24 hour urine samples w markedly higher in men than in women ($p < 0.001$) *but when the VMA excretion was* expressed in either mg/kg of body weight per 24 hrs or µg/mg creatinine there was no marked difference in the values fo men and women. Likew se accord ng to Georges & Whitby (76) the urinary excretion of VMA was 21 % higher in men than in women when calculated in mg/24 hrs, but when ex pressed in µg/mg creatinine it wa 19 % lower in men than women. Some other uthors, too, have observed no marked sex d fference in the urinary VMA excretion per 4 hrs (1 8 213 40 292 398)

Effect of psychic tension and physical exercise

In healthy air for men under test series of *actual and imagined forward accelera tions* there was a marked rise in the urinary *VMA excretion both in true and magined* situations (90). At the time of *conservativ dental care* the VMA excretio increased sign ficantly in 35 patients out of 38 (267 336) During *heart atheterization* 22 patients showed a sign ficant elevation of the VMA excretion as a result of emotional stres (263) Inexperienced *underwater swimmers* had a higher VMA excretion before diving than trained divers, evidently due to emotional tres (261).

Analogous results ha also been obtained in animal experiments. After being moved to strange cage 8 rats out of 12 had an increased excretion of VMA for 10 day (123). Handling of the rats also caused a marked increase in this excretion until the animals became accustomed to it within a week. Withdrawal of food for 12 hours raised th VMA excretion during the follow ng days (123) In the opinion of the thors, the mount of VMA excreted in the urine is *reliable index of f ndamental changes* during emotional stress. However the e motional tension in connection with 6 hours *maturation examination* which can be con

sidered to be remarkable did not cause an increase in the VMA excretion as compared to the corresponding control period (203).

Miyake *et al.* (185) examined the *post-delivery* VMA excretion from repeated samples of catheterized urine taken every 30 minutes and observed a marked rise in the VMA excretion 150—180 minutes after delivery. The VMA excretion of 45 women doing *routine household work at the end of pregnancy* (1.1 ± 0.30 S.E.M. mg/24 hrs) was only slightly higher than that of 68 mothers who were in bed rest in the obstetric unit (3.9 ± 0.20 mg/24 hrs) (197). The VMA excretion during *hospitalization* was on the average 193 ± 106 µg/hr in 5 patients with liver disease and 116 ± 71 µg/hr in 5 patients with a healthy liver but suffering from intestinal and circulatory diseases, while the VMA excretion of 30 healthy test subjects was 176 ± 68 µg/hr. The difference in the mean values of the excretions was significant between patient groups and healthy persons ($p < 0.05$ and $p < 0.02$, respectively) (27).

Both in obese persons and in female individuals of normal weight the *resting condition* decreased and *muscular work* increased the urinary excretion of VMA (285). The VMA excretion of a *basket ball team* rose during a two hours training period from 250 µg/hr to 480 µg/hr and during *contest games* from 360 to 860 µg/hr. In the latter case the initial values already were high (mean excretion of control subjects was 175 ± 68 µg/hr) undoubtedly because of tension during waiting (267). In 20 young soldiers a march of 15 kilometers caused only a very slight increase in the VMA excretion per 24 hrs in comparison to the excretion in the 24 hour control period (from 5.2 ± 0.38 mg to 5.9 mg), while heavy physical stress, a skiing tour of 60 km, caused during 12 daytime hours a more distinct rise from the control values (from 2.7 mg to 3.9 mg) (203). During the 12 nocturnal hours following the skiing tour the excretion returned to 2.1 mg, i.e. to the control level (203).

According to another investigation (316) made in connection with 60—90 km of skiing by skiers of all ages, the mean excretion of VMA in 12 hour urine was 5.3 ± 0.27 (S.E.M.) mg per 12 hrs, significantly above the control value of 2.8 ± 0.13 mg per 12 hrs ($p < 0.01$). After skiing the immediately following nocturnal VMA excretion 3.. ± 0.1 mg per 12 hrs was also significantly increased above the control value of 2.6 ± 0.11 mg per 12 hrs ($p < 0.05$).

URINARY EXCRETION OF VANILMANDELIC ACID IN PATHOLOGICAL CONDITIONS

Catecholamine-secreting tumors

Pheochromocytoma, neuroblastoma and ganglioneuroma are neoplasms that produce in addition to the adrenomedullary hormones A and NA, also their precursors dopa and dopamine and derivatives of these. These tumors develop from primitive sympathetic neuroblast (sympathogones) which normally differentiate either to chromaffin cell or to neuroblast and ganglion cells. Pheochromocytoma develops from chromaffin cell and, like its host cells, secretes both A and NA. *Neuroblastoma develops from the primitive* neuroblasts, and ganglioneuroma correspond to mature ganglion cells. The latter tumors excrete NA and dopa as well as dopamine and metabolites of these.

In cases of *pheochromocytoma*, which occurs in both children and adults and generally is benign, increased urinary excretions of A and NA were first demonstrated by Engel & v. Euler (66) by a biological method and by Pekkarinen & Pitkänen (206, 207) by a chemical method, and an increased VMA excretion by Armstrong & McMillan (7). In addition to the elevated excretion of VMA, higher excretions of also MNA and MA have later been confirmed in numerous studies and are presented in among others, many surveys of clinical and laboratory aspects (22, 60, 77, 114, 119, 285, 307, 310).

In contrast to the neuroblastoma, the excretion of dopamine or HVA is generally not increased in cases of benign pheochromocytoma (290), whereas increased excretions of dopamine and HVA seem to point to malignancy of this neoplasm (64, 82, 141, 175, 245, 260). On the other hand a normal excretion of dopa, dopamine or HVA does *not necessarily* exclude the possibility of malignant pheochromocytoma (82, 144).

The excretions of A, NA and their metabolites may show considerable individual variation in patients with pheochromocytoma

(53 54 55 56 81). For example the ratio VMA/NA+A in the urine usually is lower in the p esence of small tumor than of large ones (53 54)

Although the rise in the excretions of A, NA MNA and MA from the normal l vel i relatively greater than that of VMA patients with pheocl romocytoma (55 145) the determination of VMA seem to be the most widely used method in the diagnosis of this *neoplasm* (254 322) To attain re liable results it i well to determ ne the VMA on several successive days, particula ly in the p esence of pa oxysmal h pertens n In certain borderline cases determinat on of MNA, MA nd/or A and NA as well a other pharmac logical tests are alw needed in addition to determination of VMA (53 67 77 226 253 322)

Mason *et al* (180) were the first to observ increased excretions of A and NA in cases of *neuroblastoma* and Sandler & R thven (257) demonstrated an elevated excret on I VMA in two cases of neuroblastoma G een berg & Ga dner (102) ganglioneuroma nd Stickler *et al* (28) in ganglioneur blastoma

Due to diagnostic difficulties and the rel atively rare occurrence of these types of tumor t i not yet exactly known how often the VMA excretion increased in thei presence Many a thors ha e observed nor mal excretions in patients w th neuro blastoma (19 24 105 131 133 155 293 300 312, 314) but the proportion of such cases is clearly under 25 % in most series. So for in tance only one of 25 patient had the VMA excretion within normal l mit in the neuroblastoma series of Studnitz (293) 5 out of 26 in that of *Voorhess et al* (315) one of 16 in Robinson (242) and only 4 of 73 in Käser s (130) series.

In *ganglioneuroma* a benign tumo en countered mostly in adults but occasionally also n ch ldren, increased VMA excretion have been comparatively seldom described (86 100 102, 151 251 279 340) In Käser s (130) series 6 out of 8 had normal values, as also had all the 5 patients with ganglio-neuroma examined by Studnitz (295)

Ganglioneuroblastoma is histopathologically an termediate form of neuroblastoma and ganglioneuroma reflected also in the ganglio neuroblastoma s hormonal excretion pattern of the metabolites of catecholamines. Thus, fo instance these tumors excrete frequently clear l higher amou ts of VMA than the ganglio-neuromas but less than the neuroblastoma (86 130 151 787 797 300, 313 314 310)

In view of the malignancy of neuroblastoma n earl diagno is s important. By determin ing also HVA and/o dopam ne in addition to VMA a correct diagnosi can be reached in nearly every case (53 130 326) Si m ltaneous *determinations of VMA and total* catecholamines will lso lead to a diagnos s of neuroblastoma w th h gh degree of accuracy U ing Gitlow s screening test (85) for the determination of VMA and his own total catecholamine screening determination, Bell 18) was able to make n his series a diagno is of neuroblastoma w th the ac uracy of 100 per cent

The relationship between the cl nical mptom of the neoplasms of neural origin, such as hronic diarrhea and hypertension and the catecholam nes and thei metabolites produced by these neoplasms s not clear (4 130 310) Obviously these s mptoms are as soci ted more f equently with differentiated than w th ndifferentiated tumors and result from the tumor since they disappear after removal of the neoplasm (99 100 124 134 151 154 180 251 79 282 289 297 314)

As other pecial cl ical haracteristics Chatten & Voorhess (44) reported 6 known instances of familial occurrence of neuro-blastoma. Griffin & Bolande (107) followed p two sisters among these patients, both of whom showed progression of their etro peritoneal tumors to ganglioneuroma In one case metastatic tumor nodules of the skin which had matured to ganglioneuroma came to closely resemble neurofibroma through con tinued loss of ganglion cells. A 3-year-old child with ganglioneuroblastoma exhibited the clinical features of myasthenia gravis, which disappeared after excision of the tumor (241).

Surgical operations

Three *child en* showed postoperatively no rise in the urinary excretion of VMA accord ing to McKendrick & Edwards (174)

In *adults*, however ncreased VMA excre tions have been seen after surgical operations

sidered to be remarkable did not cause an increase in the VMA excretion as compared to the corresponding control period (303)

Miyake *et al* (185) examined the *post delivery* VMA excretion from repeated samples of catheterized urine taken every 30 minutes and observed a marked rise in the VMA excretion 150—180 minutes after delivery. The VMA excretion of 45 women doing *routine household work at the end of pregnancy* (4 4 ± 0 30 S.E.M mg/24 hrs) was only slightly higher than that of 68 mothers who were in bed rest in the obstetric unit (3 9 ± 0 20 mg/24 hrs) (197) The VMA excretion during *hospitalization* was on the average 1 3 ± 106 μg/hr in 5 patient with liver disease and 120 ± 71 μg/hr in 5 patient with a healthy liver but suffering from intestinal and circulatory diseases, while the VMA excretion of 30 healthy test subjects was 176 ± 68 μg/hr The difference in the mean values of the excretions was significant between patient groups and healthy persons ($p < 0.05$ and $p < 0.02$, respectively) (7)

Both in obese persons and in female individuals of normal weight, the *resting condition* decreased and *muscular work* increased the urinary excretion of VMA (283) The VMA excretion of a *basket ball team* rose during a two hours training period from 250 μg/hr to 480 μg/hr and during *contest games* from 360 to 860 μg/hr In the latter case the initial values already were high (mean excretion of control subjects was 175 ± 68 μg/hr), undoubtedly because of tension during waiting (267) In 20 young soldiers a march of 15 kilometers caused only a very slight increase in the VMA excretion per 24 hrs in comparison to the excretion in the 24 hour control period (from 5 2 ± 0 38 mg to 5 9 mg) while heavy physical stress, a skiing tour of 60 km, caused during 12 daytime hours a more distinct rise from the control values (from 2 7 mg to 3 9 mg) (203). During the 12 nocturnal hours following the skiing tour the excretion returned to 2 1 mg i e to the control level (203

According to another investigation (316) made in connection with 60—90 km of skiing by skiers of all ages, the mean excretion of VMA in 12 hour urine was 3 3 ± 0 27 (S E M) mg per 12 hrs, significantly above the control value of 8 ± 0 15 mg per 12 hrs ($p < 0.01$) After skiing the immediately following nocturnal VMA excretion, 3 ± 0 mg per 1 hrs, was also significantly increased above the control value of 2.6 ± 0 mg per 12 hrs ($p < 0.05$)

URINARY EXCRETION OF VANILMANDELIC ACID IN PATHOLOGICAL CONDITIONS

Catecholamine secreting tumors

Pheochromocytoma, neuroblastoma and ganglioneuroma are neoplasms that produce in addition to the adrenomedullary hormones A and NA, also their precursors dopa and dopamine and derivatives of these These tumors develop from primitive sympathetic neuroblast (sympathogones) which normally differentiate either to chromaffin cells or to neuroblasts and ganglion cells. Pheochromocytoma develops from chromaffin cells and like its host cells, secretes both A and NA. Neuroblastoma develops from the primitive neuroblasts, and ganglioneuroma corresponds to mature ganglion cells. The latter tumors excrete NA and dopa as well as dopamine and metabolites of these

In cases of *pheochromocytoma*, which occurs in both children and adults and generally is benign increased urinary excretions of A and NA were first demonstrated by Engel & v Euler (66) by a biological method and by Pekkarinen & Pitkänen (206 20 by a chemical method, and an increased VMA excretion by Armstrong & McMillan (7). In addition to the elevated excretion of VMA, higher excretions of also MNA and MA have later been confirmed in numerous studies and are presented in among other many surveys of clinical and laboratory aspects (22 60 77 114 119 285 307 310

In contrast to the neuroblastoma the excretion of dopamine or HVA is generally not increased in cases of benign pheochromocytoma (290) whereas increased excretions of dopamine and HVA seem to point to malignancy of this neoplasm (64 82 11 175 245 260) On the other hand, a normal excretion of dopa, dopamine or HVA does not necessarily exclude the possibility of malignant pheochromocytoma (82 144).

The excretions of A, NA and their metabolites may show considerable individual variation in patients with pheochromocytoma

fa lure had no statistically significant effect on the mean VMA excretio Unl ke the series mentioned, that of Chidsey *et al.* (45) showed no sign ficant rise in the excretion of VMA in patients with heart failure

Respiratory diseases

In 12 premature infants with the *respiratory distress syndrome* (RDS) the plasma A level was fourfold, whereas no significant rise was noted in the plasma NA (46) According to Cheek & Rowe (47) A is of major significance in the pathogenesis of this disease However in the study of Boehm & O Brien (25 n greater VMA excretions were found in the newborn with RDS than in the control children.

The A and NA excretions of *asthmatic* children were greatly ncreased n Koleso study (153) and were p oportionate to th severity of the paroxysm. The excret on of A by one of the patients during a severe attack wa 100 fold the normal W th im pro ement of the condit n th ex etion were normalized (153) A imilar observ t on w made earl er concern g asthmatic adult by Knauff *et al.* (149) n whom, h wever the ncrease of NA was greater than that of A In good greement with these f ndings is the observation of increased VMA ex cretion in severely ill patients with *respiratory insufficiency* (81) nd the same concern som of the asthma patients of H tzenberger & Burklen (117)

Hepatic diseases

I *portal cirrhosis* of the liver the formation of VMA from dministered rad oa ti NA nd MNA was reduced from the normal a d a ignificant ise was noted the sulfate conjugates of NA and MNA (95) Th study revealed sl ght eduction MAO activity However the oxidativ deam ination of b ological amines has been normal n some other studies of patient with liver diseases (269 271) also the VMA excretion of patients with cirrhosis of the liver has been normal (215) Likewise the VMA ex cret on of hospitalized patients w th liver diseases was similar to that n patients with intestinal o c ulatory diseases but w thout liver d sease (72)

Renal diseases

Reduced VMA excretion has been ob served in adults with *renal insufficiency* (202, 203 214 270) Pekkarinen & Iisalo (202) found that the VMA excretion decreased with an increasing serum creatinine level and concluded that th educed VMA excretion n kidney d seases was due to low enal clearanc of VMA.

Some hormonal diseases

In *hyperthyroidism* the VMA excretion was either normal (1 5 327) or to some extent lowered (171 215) In *hypothyroidism* normal VMA excretions were observed (1 5 3 7) In the study by Brunjes *et al.* (30) reduced VMA excretions were seen n both h po and hyper th roidism nd the MA+MNA/VMA ratio wa ncreased in hyperthyroidism

I *diabetes* Petrášek & Dubovský (215) demonstrated a normal VMA excretion in 10 patients Ten diabetics out of 22 n Floch s series (72) showed a rise in VMA excretion in l nical ond tions in which there was ery l ttle or no glucose in the urine five having a maximum VMA content of 10—25 µg/ml in the urine and five over 30 µg/ml.

Sulfonyl ure caused rises the VMA and VA excretions in diabetics and both in tra enous admin stered ACTH and endoge nously released ACTH in the metyrapone test caused an ncrease of the VMA and VA excretions in diabetics as compared with healthy ndividuals or with persons with latent diabetes (335) On the basis of thei results the uthors suggested that th sympathoadrenomedullary system of diabetics reacts more strongly to both exogenous and endogenous ACTH than that of other individuals.

Disorders of the autonomic nervous system

In 11 child en with *dysautonomia* (Riley Day syndrome) the HVA excretion w s twofold the normal nd th VMA excretion onl half of the normal (281). Simila f ndings h been published by Gelzer *et al.* (75) n newborn patient and by Gitlow *et al* (84) in 40 patient with dysa tonomia.

In contrast to the above the VMA excretion was within normal limits in two patients with dysautonomia in the series of Young *et al.* (310) and in four patients in the series of Greer & William (106).

A disturbed catecholamine metabolism has been demonstrated also in *phenylketonuria* in which there were reduced urinary excretions of dopamine, A and NA (183). In phenylketonuria, as in dysautonomia, the plasma levels of endogenous A and NA are deficient and both have an increased sensitivity to injections of A and NA (40, 75, 129, 188, 280).

Elevated A, NA and VMA excretions have been demonstrated in *infantile acrodynia* (17, 239). The probable etiological base of this disease is mercury poisoning (69, 319). Mercury inhibits S-adenosyl methionine (11) and thus has an inhibitory effect on meta-O-methylation and potentiates the effect of adrenaline (45).

In *orthostatic hypotension* a change in the NA metabolism has been noted in which the urinary excretions of methylated catabolites, for instance of VMA and conjugated MNA and MHPG, are increased and those of non-methylated catabolites, for example DHMA and 3,4-dihydroxyphenylglycol sulfate, are reduced (94). A patient of Gelber *et al.* (75) with postural hypotension showed no alteration in the VMA excretion on change of position from supine to standing. Increase of VMA excretion has been observed in *Burger's disease* and *Raynaud's syndrome* (196).

Neurological and mental diseases

Patients having complete *transverse lesion of the cervical cord or the upper thoracic cord* (above Th V) have been observed to have a reduced blood pressure and a low urinary VMA excretion (122, 244). Ortho... caused a rise in VMA excretion in healthy persons and in persons with *lesions of the lower spinal cord* (below Th V); this ... absent ... high lesions (1..). Schmid *et al.* (272) found in their series the lowest VMA excretion (0.1—0.6 mg/24 hrs) in four patients with ... plegia.

Th... 1 VMA was normal in 15 patients with *extrapyramidal disorders* in the form of ... and/or athetosis, but HVA was significantly decreased (235, 38).

In patients with Parkinson's disease or other hyperkinetic conditions the urinary VMA and HVA excretions were normal both before and 4— days after stereotactic thalamotomy (23, 235). HVA in the cerebrospinal fluid was decreased in patients with Parkinson's disease (34, 37) but increased in patients with chorea [Birkmayer & Hornykiewicz, cited by Birkmayer (*1)].

The urinary excretion of VMA by schizophrenic was normal (171, 2?0) and the same was true according to LaBrosse *et al.* (167) ... the main metabolites of Iv. administered H... In contrast McDonald & Weise (175) found in 10 schizophrenics an elevated VMA excretion, and a similar observation was made by Pscheidt *et al.* (24) in *acute psychotic exacerbation*.

Histamine injection ... significantly raised the excretion of VMA in male but not female schizophrenics (150).

Three patients with *acute periodic catatonia* showed greatly increased VMA, NA and MNA excretion during psychotic attacks; during clinically symptomless periods the excretion were mainly within normal limits (57). During attacks of *migraine* there was an increase in the excretions of 5-hydroxyindoleacetic acid (5-HIAA) and VMA (57, 5.., 276). Sicuteri *et al.* (276) noted VMA excretions of up to 1? mg per 24 hrs, which reverted to normal with convalescence.

Other diseases

According to Matsaniotis *et al.* (181) *chronically anemic children* put out almost twice as much VMA as did healthy children when the excretion was related to body weight.

Decreased urinary excretion of VMA was seen in 19 children with *rheumatic fever and other collagen diseases* as compared to 16 controls; methylcatecholamines also were low, though this was less pronounced (49). According to the authors these results suggest decreased monoamino-oxidase activity in the patients.

Increased excretion of VMA has also been reported in association with a *retinoblastoma* (154), a *carotid body tumor* (90) and *malignant carcinoid tumors* (179, 294). In a case of malignant carcinoid tumor the highest value for VMA excretion was only twice that of the upper limit of normal whereas the output of 5-HIAA was 70 fold the normal

level (179) The urinary VMA excretion of patients with pulmonary carcinoma metastases was significantly higher than that of other carcinoma patients, the latter being with n the normal range (1 1)

In male patient with *glauc ma* the ex cretion of VMA w decre sed (6)

Effect of drugs or diet

The result I investig ti n o er g th effect of ertain drugs on the na cret on f VMA ar sh w i in Table 5

The intak of coffee tea tru fruit d especially of food ontaining anill ha generally not been permitted in connect on w th VMA determinations since they may lead to erroneous results in most methods The sam restriction ha been made nce r ing bana ia because of their high o tent of no d al i and dopamine (317) These food and bev erages do not, however affect VMA deter m nat ns mad b the method of Pisan *et al* (2 1 56 300 3 7) However t ha ecentl been demonstrated that an mount of instant offee equivalent to 16 mg f c ffeine sed the urinary VMA xcret n to more than twofold during the follow ng 4 ho rs (334)

STABILITY OF VANILMANDELIC ACID IN THE URINE

N l of VMA was observed d ring 7 nc l n four urine samples stored n the deep f ez t —20 °C (992) Neither wa n gnificant ha ge noted in our p esent tud n d VMA o tent of urine samples 10 samples, pH —3) after storage in th el iger t —5 up to 4 months and f ezi g nd melt g d th samples th ee times 199) G tlow *et al* (80) observed that urinary VMA mained table fo several m ths at 10 C when the pH of the samples was 3—4 U de the same ond tions the standard VMA

Table 5 *Effect of drugs on urinary VMA excretion*

Increased VMA excretion		Decreased VMA excretion		No consistent influence	
ACTH)	(335)	Alpha-methyl-p tyros ne	(277)	Alloxan)	(192)
Adrenaline, oral	(230)	Bretylium tosylat	(1"0)	Amphetamine	(173)
Adrenaline, parenteral	(96, 97 116)	Catapresan ®	(120)	Angiotensin	(509)
Caffeine	(334)	Chlorpromazine, sh rt term	(173)	Ephedrine, nasal	(80)
Glucagon	(337)	Chlorpromazine long term)	(25)	Guanethidine	(330)
Histamine	(150 303)	Imipramine, long-term	("66)	Isoprenaline, subl inhal	(80, 255)
Hydrocortisone)	(192)	Iproniazid	(11 93, 95, 146, 231 249 264 291 333)	Mebrobamate	(173)
Insulin (hypoglycemia)	(192, 296, 337)	Isocarboxazid	("74)	Morphine	(175)
Metyrapone)	(335)	Methyldopa)	(72 136, 265)	Naphazoline, nasal	(80)
P enylamine, short term	(165)	Nialamid	(209)	Noradrenaline, oral	(255)
Reserpine, short-term	(5, 173)	N isopropyl p nitrophenyl-ethanol amine	(34)	Norad enaline, i.	(509)
T lbutamid	(333)	N troglycerin, subl	(35)	Oxedrine tartrate, oral	(162)
		Oxypertine, long-term	(236)	Pargyline	(29)
		Phenelzine	(85, 266)	Pentobarbital	(173)
		Prenylamine, long term	(205, 229)	Phenylephrine	(80)
		Psilocybin	("78)	Thyroxi)	(192)
		Reserpine, long term***)	(2 25 228)		

) I diabetics only

**) Experimental animal

) I patients with hypertension inconsistent results in other diseases (35, 74, 135 136 275, 326)

**) N effect according t one investigator (228)

) Consistent changes not observed by som investigat ors (29, 330)

) Experimental animals

solution remained stable for over a year. According to v. Studnitz (292) the urinary VMA was unchanged during 8 days at +4 and +20 C also without the addition of acid. Jacobs *et al.* (128) report that there was no significant difference between samples stored for one week with or without preservative (bisulfite fluoride) in the refrigerator (+4 C) and at room temperature (+25°C). Sato *et al.* (26 again observed that in urine stored withou acid at +15°C the loss of VMA began o the 4th day and by the 7th day was in som cases as much as 70 %. In an infected urin sample kept at +4 — +20°C no VMA wha soever could be demonstrated by chromatog raphy (73).

PURPOSE OF STUDY

The main objects of the present investigation were as follows

1 To determine the normal VMA excretion in the urine during different age period of childhood and in certain cond tion of new born infants, as well as to observe a possible sex difference and diurnal hythm of VMA excretion in children over 2 ears of age)

2. To determine the urinary excretion of VMA
   a) in certain diseases n children in wh h differences ha e earlier been noted the excretions by ad lts of A and NA or their metabolites, e g m pediatric patients with neural tumors" heart failure bronchial asthma and after surgical operations,

   b) in ther diseases of children, mainly with a iew to finding diseases n which the urinary excret on of anil mandelic acid possibl is increased o decreased

1) Children under 2 ear er excluded because of the technical difficulties in urine ollection especiall from female infants

MATERIAL AND METHODS

The series of children studied is divided into two parts (Table 4)

1 *Children in normal conditions* which comprises 389 children and their 735 urine samples.

Besides healthy children, a group comprised of 64 selected hospitalized children between 1 week and 24 months of age has for practical reasons been taken into this part (included in the above figures) and because of lack of normal material of corresponding age [1] is used as a control for some patient groups. With certain reservations it illustrates the VMA excretion of children of this age

2 *Children with certain pathological conditions* comprising 230 patients and their 4[illegible] urine samples.

The total number of children studied was 619 and number of urine samples examined was 1157

CHILDREN IN NORMAL CONDITIONS

Newborn infants

Fullterm male infants — These healthy babies (n=64) were from the newborn wards in the Department of Obstetrics of the University of Turku No female infants were included because of the technical difficulties in urine collection. The 24 hour urine collections for the VMA determinations were made on the 1st and 2nd as well as on the 3rd and 4th days of life. The collections took place in the newborn wards, where the room temperature was maintained at 24—26 C. The newborn infants were brought to their mothers rooms for feeding only

The fullterm newborn infants fall into the following three groups a) 30 healthy newborn infants (=controls) b) 47 healthy newborn infants divided into two groups according to the duration of the second stage of delivery i e "short second stage (—10 minutes, mean 7 minutes) and "long" second stage (11—60 minutes, mean 25 minutes) In these infants the effect of the duration of the second stage of delivery on the VMA secretion was studied The group consisted of all the normal fullterm newborn infants in group a) and of 17 selected newborn infants at whose birth the second stage of delivery had lasted more than 90 minutes c) 17 healthy newborn infants delivered by cesarean section.

Premature male infants. — These babies (n=41) were from the Children s Hospitals of the Universities of Turku and Oulu All of them were in a good condition during the urine collection period. The care was the normal routine for prematures a few babies were treated in an incubator Female infants were not included because of the difficulties in urine collection.

Children between 1 week and 15 years [1]

Selected hospitalized children 1 week to 24 months of age comprised 64 patients (14 girls and 50 boys) in the Children s Hospital of the University of Turku divided further according to age into three groups 7—30 days, 1—6 months and 6—24 months These children were selected by eliminating all children subjected to surgical operation or affected with diseases such as heart failure bronchial asthma febrile infection respiratory distress syndrome of the newborn, hepatic or renal disease or disease causing dehydration. They were therefore assumed to have a

1 The urine collections during 48 hours from children of this age described in detail on page [illegible] cannot be performed in a reliable manner at home

1 [illegible] but not 15 [illegible] Other similar expressions of age are analogous

Table 4 *Total material studied age groups of children in normal and pathological conditions series sex distribution and number of urine samples for UMA determination*

	Age groups		Normal conditions: Number of children Total	F	M	No. of samples	Pathological conditions: Age groups	No. of patients	No. of samples
1	Fullterm infents 1—5 ds		64		64	2.2	1—4 ds	25	50
							4—7	21	42
2.	Prematures —31 d		41		41	93			
	Range	Mea							
3)	7—30 ds	19 2	18	2	16	33	—30 ds	5	10
	1—6 mos	2 5	19	2	17	35	1—6 mos	*0	36
	6—24	11.5	27	10	17	47	6— 4	8	15
4.	2—4 yrs**)		41	24	17	65	—4 yrs	17	47
	4—6	4 8	19	9	10	19	4—6	30	46
	6—8	6.9	23	11	12	23	6—8	1	43
	8—10	8 9	19	11	8	19	8—10	21	33
	10—12	11.2	19	7	12	19	10—12	24	40
	12—15	13 8	43	2.	21	43	12—15	38	55
5.	Other groups		56	5	51	117			
	Total		359	103	266	735	Total	230	422

) Th ge groups f selected hospitalized ch ld en
**) Two years and over but not yet 4 Other similar expressions l g are analogous

relatively normal excretion of VMA nd be able to serve a part of the ont l series for hospitalized ch ldren sinc no la t was present that is known t ha n flect on the VMA excretion.

Healthy children between 2 and 15 years (84 girls and 80 boys) — Those under 8 years of age were at the time of the study n municipal k ndergartens or day urseries n Turku and those 8—15 years of age were primary school pupils in Varkaus The urin collections in th pa t of the normal series wer made mainly in April—May or October—November and the temperat re in these period w the relatively even, neutral one pre vailing in interseasons. Eight of the children 6—8 years of age were in umme colony and ther samples were ollected idsummer

Other groups. — F fty six physically healthy children of different ages wer studied homes, schools, reform schools, summer olonies and the children ps chiatric n of the Central Hospital of Kuopio Th 24 hour urinary VMA excretion of the reform school boy (T ble 10) was studied a cold and a warm season (in January nd at the end of M i d other child en wer part of th st dy of d nal ari tions n VMA excretion T ble 9 F g 5)

CHILDREN WITH CERTAIN PATHOLOGICAL CONDITIONS

Tl series of 230 ch ld en wa compiled n part selected and i part arbitrarily of pat ent dmitted to the Children' Hosp tal f t Univers ty of Turk The group of patient (n=163) with diseases that re of particula nterest for the subject of th s t dy described in detail below following mainly the order used n presenti g the findings in the "Results" chapter

a) *Neuroblast ma* (on ch'ld) and *pheochromo cytoma* (one ch ld) — The case report are given in the "Results" chapter

b) *Surgical operations* — This group con sisted of 4 operated children 3 month to 14 rs of g four of whom were under 2 years of age Collection of 24 hour urine samples was generally begun on the morning following the operat on (= 1st postoperative day) and they were collected during 1—2 day (Tabl 11)

c) *Congenital heart disease with or without heart failure* — This group consisted of 20 children aged 1 day and over but under 15 years 11 were under 1 year (Table 1) Three children of early infancy age were examined twice and one three times at different times of treatment and at different ages The results of 25 samples are therefore given, 11 of which were representative of heart failure 6 of compensated heart failure and 8 of congenital heart disease without heart failure The criteria for heart failure were a mean respiratory rate of 60 per minute (in 7 out of the 11 examinations) and/or systemic edema. Furthermore enlargement of the heart was found in 9 of the 11 instances.

d) *Febrile infections* — On 9 children with febrile diseases 5 month to 8 years of age 5 urinary VMA determinations were made on successive days and mean axillar or rectal measurements of body temperature were noted on the same days. Details of the group are as follows *Urinary VMA determinations* were performed on 5 patients 3—8 years old with measles on 3 successive days after appearance of the rash on 3 children 5 months to 4 years of age with acute purulent meningitis on 2—3 days and on one child 8 years of age with acute pyelonephritis and a *normal level of urea nitrogen on 3 successive days.*

e) *Acute bronchial asthma.* — From 7 non febrile hospitalized children 2—14 years of age with acute bronchial asthma 8 hour urine samples were collected during the first 24 hours after admission to hospital and 24 hour urine samples on the following 1—2 days. During the first day in hospital the patients were moderately or severely dyspneic and the clinical state was almost unchanged, on the 2nd day the dyspnea was mild and on the 3rd day the children were nearly free from symptoms

F asthma pa ts re d theophylline phedrine od potassium iodide med at on during the time of urine collection One pa nt d dd small 15 mg of hlorpromazine m he 1 day of ne collection, nd one pa ient was given 10 mg of hlorpromazine m 16 hour befor urine ollection 25 mg 3 of hydrocortisone m on he f st day of urine ollection and 5 mg 3 of prednisolone pe os on he se ond da

f) *Exchange transfusion for hemolytic dise[ase] of the newborn* — In 8 newborn infan[ts] with hemolytic disease who had been giv[en] an exchange transfusion on the first day [of] life the urinary VMA determination was ma[de] on the second day

g) The VMA excretion was studied in [a] 15 year old boy with *chorea minor* a 9 yea[r] old girl with *paraplegia of the lower e[xtremities]* 4 children 8 months to 9 years [of] age with *hepatic disease* 5 children 6 mont[hs] to 11 years of age with *renal disease* and children 1—3 months of age with *congen[ital] pyloric stenosis* From the last mentioned t[he] urine was collected preoperatively except fro[m] one child on the 3rd and one on the 6[th] day *after Ramstedt's pyloromyotomy* and 6 these children received isopropone bromide medication during collection

h) *Respiratory distress syndrome (RDS) of t[he] newborn.* — The VMA excretion was studi[ed] on 2—3 days in 13 newborn infants 1—5 da[ys] of age who had a moderate or mild RD[S] (Table 13) *The mean daily respiratory ra[te]* for evaluation of the respiratory difficul[ty] was determined on the same days.

i) *Hormonal and metabolic diseases* — T[he] VMA excretion was studied in 17 childr[en] with diabetes mellitus 2—14 years of age a[nd] in one child 1 month old

I 10 se he disease had just be diagnosed insulin had bee g en 1—3 days only) 3 hildren th old diabetes had history of 1 mon[th] to 13 ars. At he time of his investigat on 10 hildr[en] had moder te or sev ke oacidosis, wh le as mo[...] or absent in he other hild The urinary exc[retion] of glucose on th days of VMA study determine[d] f om all he hildren

Eighteen children with various other hormona[l] or metabolic diseases are presented in Table 14

j) *Other diseases.* — This group include[s] a small number of patients with *nephros[is]* (n=7) *progressive muscular dystrophy* (n=3) o[r] *neurological* (n=9) *psychiatric or psychosomati[c] diseases* (n=5)

For this "pathological conditions" part a[n] additional 67 child patients were examine[d] who were not included in the groups mentione[d] above Most of these patients were hosp talize[d] for examination only owing to variou[s] diagnoses, such as constipation, abdominal pain headache etc., or they had a slight infection like sinuitis, recidivous bronchitis, etc.

TECHNIQUE OF URINE COLLECTION

All samples of urine were collected a 24 hour samples w th the exception of the 8 and 12 hour collections carried out for studying the night and day excretions and the excretions of patients with asthma.

During the collection day th rine w stored in bottles conta ning 0 5 ml of 6 N hydrochloric acid for every 100 ml of rin expected The bottles were kept in a oo l place At the end of the 4 l o per od l collection the urine was measured the sampl to be studied was poured into a test t be and if necessary hydrochloric acid wa dde d to adjust the pH to about 2 Th tube wer then carefully closed and stored at +4°C o er night or —5°C fo longer periods.

In the case of the hospital patient th urine was collected 1—2 day after dm io except when there was some cut d se se (bronchial sthma, febrile fection) in which the excretion during the acute pha w of special interest. From infant who oul l not yet control their urination the urin was collected into Coloplast) bags which were emptied several times a day t th acidified storage bottles. In nearly every case the urine was ollected during two suc es 24 hour periods. Collection from the older children w s made in most cases during one 24 hour period only The technique of urine collection at home was explained to the children who were ble to understand t nd alway to the parents n dd tion, detailed printed i structions wer handed to them. The col lections from hosp talized patient wer per formed by the nursing staff who had been nformed of the technique Medication de man led b the child disease and given previou to or during the period of urine ollect o wa noted down Ther were no dietar est ti n during the collection pe riod

I general the tored frozen urine samples wer examined w d 1—4 weeks fter col lecti on After certain mp ovements in the mi omethod had been made a small part l the u ine samples collected in the ea l part l he tudy from both the clinical and the mal series were -examined 7—12 mo tl fter ollection

1) Dansk Coloplast, 4 Bronzevej, 3060 Espergaard, Denmark

DETERMINATION OF URINARY VANILMANDELIC ACID

Th nilma delic acid was determined b mean of the micromodification by Pekkarinen & H kulinen (199) of the method of Pisano *et al* (221) This micromethod and the reliability criteria of the VMA determ nation re described in the Appendix.

STATISTICAL TREATMENT

In order to draw tatistical conclusions, the mean, standard error of the mean and standard deviation were calculated[1].

Student t test was used to study the statistical d fference between two means. Th difference is said to be significant if $p \leq 0.05$ The dispersions stated in the text are expressed as S E.M

1 Performed by Tauno Pasanen, M Sc

RESULTS

URINARY EXCRETION OF VANIL MANDELIC ACID IN NORMAL CONDITIONS

Age groups between birth and 15 years

Newborn infants

The daily mean urinary excretion of VMA by healthy *fullterm infants delivered by the vaginal route* increased significantly (p 0.001) from 0.13 ± 0.01 mg per 24 hrs on *the first day of life* (30 urine samples) 0.50 ± 0.0 mg per 24 hrs on the fifth d (16 samples), and respectively from 33 ± to 84 ± 5 μg/kg body weight per 4 h ($p < 0.001$) (Table 5 Fig 2).

During the same period there wa significant decrease in the mean content VMA from 4.9 to 1.5 μg per ml of uri

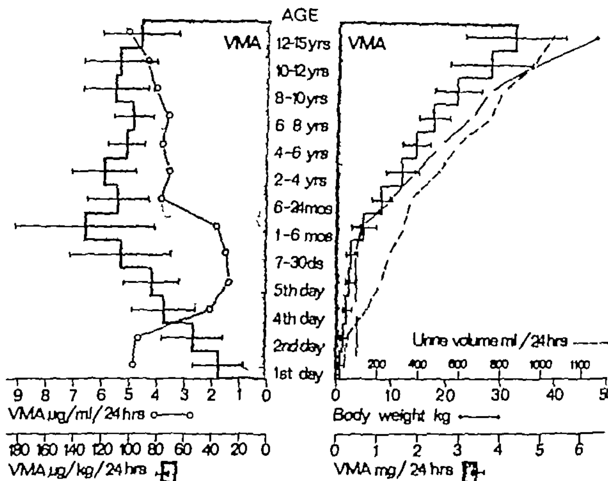


Fig. 2. Mean VMA excretion (left: μg/ml per 24 hrs and μg/kg per 24 hrs; right: mg/24 hrs), mean urine volume (ml/24 hrs) and mean body weight (kg) of healthy children in different age groups between birth and 15 years. Children in the age groups of 7—30 days, 1—6 months and 6—24 months are selected hospitalized children. Dispersion=1 SD

Table 5 *Mean urinary UMA excretions (mg/24 hrs g/kg/24 hrs µg/ml/24 hrs) and mean urine volumes (ml/24 hrs) of healthy children in different age groups between birth and 15 years Children in the age groups of 7—30 days 1—6 months and 6—24 months are selected hospitalis ed children*

Age, range (mean)	1st day	2nd day	4th day	5th day	7—30 ds (13 2)	1—6 mos (2.5)	6—24 mos (11.3)	2—4 yrs (2 9)	4—6 yrs (4.3)	6—9 yrs (6 9)	8—10 yrs (8.9)	10—12 yrs (11.2)	12—15 yrs (13.8)
Mean weight, kg	3 7	3 7	3.5	3 6	3 3	4 7	0 9	13 8	18 7	4	7	35	47
No. of children	30	29	23	16	18	19	27	41	19	3	19	10	43
					VMA mg/24 h								
Mean	0.13	0.20	0.26	0.30	0 35	0 64	1 09	1 61	1 93	2 33	2 93	3 73	4 76
S D	±0 07	±0 09	±0 09	±0 09	±0 12	±0 29	±0 24	±0 38	±0.34	±0 33	±0.6	±1.01	±1 19
S.E.M.	±0.01	±0 02	±0.02	±0 02	±0 03	±0 07	±0 05	±0 06	±0 09	±0 09	±0 13	±0 3	±0 18
					VMA µg/kg/24 h								
Mean	35	54	75	84	107	132	109	118	102	97	110	107	0
S D	±18	±22	±23	±20	±36	±50	±2	±23	±13	±14	± 9	±26	±27
S E M.	±4	±4	±5	±5	±8	±11	±4	±4	±3	±3	±5	±6	±4
					VMA, µg/ml/24 h								
Mean	4 9	4.7	2.1	1.5	1.5	1 9	3.9	3 6	3 8	3 6	4 1	4 4	5 1
S E.M.	±2.6	±2.2	±1 1	±0.4	±0 8	±0.8	±1.8	±1.3	±1 3	±1 2	±1 2	±1 2	±2 0
S.D.	±0.7	±0.6	±0.2	±0 1	±0.2	±0 2	±0.4	±0 2	±0.3	±0 3	±0 3	±0 3	±0 3
					Urine volume ml/24 h								
Mean	31	51	146	205	255	390	321	478	551	17	771	897	910
S.D.	±19	±33	±57	±40	±94	±89	±130	±17	±186	±270	± 46	±337	±378
S.E.M.	±4	±6	±12	±10	±22	±20	±25	± 7	±39	±56	±56	±73	±58

per 24 hrs ($p<0.001$). The mean urine volume increased from the 1st to 5th day from 31 to 70 ml per 24 hrs.

In healthy male babies *delivered by cesarean section* no marked differences from the above group were noted in the mean excretion of urinary VMA (Fig. 3).

Neither had the *duration of the second stage of delivery* any significant effect on the VMA excretion when the two subgroups, i.e. "long" duration of II stage of delivery (mean 25 min) and "short" duration of II stage of delivery (mean 7 min) were compared (Fig. 3).

In the group of healthy male *premature newborn* (mean weight 1.8 kg) the mean excretion of VMA rose significantly ($p<0.05$) from the 2nd to 6th day of life, i.e. from 0.05 ± 0.01 to 0.15 ± 0.0 mg per 24 hrs (mean of 8–19 urine samples per day) (Table 6, Fig. 3). The daily mean excretion of VMA amounted thus to *about 50 % of that* of the fullterm newborn, but in relation to body weight the VMA excretion on these days was the same as that of the fullterm normally delivered newborn, and on the 6th day of life it was twice that of the 2nd day.

The mean VMA content of urine dropped significantly on the 2nd to 6th days from 1.9 ± 0.6 to $1. \pm 0.1$ µg/ml per 24 hrs ($p < 0.05$), i.e., only slightly from the originally low reading as compared to the fullterm newborn.

On the 2nd day of life the mean urine volume of premature newborn was 49 ml per 24 hrs and thus was as high as in the fullterm group. On the other hand whereas the mean amount in the latter group was on the 5th day fourfold (105 ml) that of the 2nd day, it was only twofold (102 ml) in the premature group.

The 7 *prematures 11–16 days of age* (mean 14 days, mean weight 2.0 kg) had a total mean VMA excretion of 0.20 ± 0.02 mg per 24 hrs (14 urine samples). The mean VMA excretion of 103 ± 11 µg/kg of body weight per 24 hrs proved to be the same as in the "normal" control group 7–30 days of age (mean 15 days).

The 10 *prematures 21–31 days old* (mean 27.4 days, mean weight 2.1 kg) had a total mean VMA excretion of 0.33 ± 0.03 mg per 24 hrs (17 samples) and 156 ± 10 µg/kg of body weight per 24 hrs. The latter value was significantly higher ($p < 0.01$) than those in groups of two weeks mean age of both prematures and "normal" control infants (cf. page 33 and Table 5).

Table 6. *Mean urinary VMA excretions (mg/24 hrs, µg/kg/24 hrs, µg/ml/24 hrs) and mean urine volumes (ml/24 hrs) of premature male infants during the first month of life*

Age, days	2nd	3rd	4th	5th	6th	11–16 (14.0)	21–31 (27.4)
Mean weight, kg	1.8	1.9	1.7	1.7	1.8	2.0	2.1
No. of infants	9	8	19	19	11	7	10
No. of urine samples	9	8	19	19	11	14	17
VMA, mg/24 h							
Mean	0.05	0.12	0.12	0.14	0.15	0.20	0.33
S.D.	±0.03	±0.05	±0.04	±0.07	±0.06	±0.05	±0.09
S.E.M.	±0.01	±0.02	±0.01	±0.02	±0.02	±0.02	±0.03
VMA, µg/kg/24 h							
Mean	43	60	72	81	87	103	156
S.D.	±16	±24	±22	±40	±34	±49	±32
S.E.M.	±5	±8	±5	±9	±10	±11	±10
VMA, µg/ml/24 h							
Mean	1.9	1.7	1.6	1.6	1.2	1.1	1.3
S.D.	±1.7	±1.0	±0.8	±1.0	±0.4	±0.[illegible]	±0.3
S.E.M.	±0.6	±0.3	±0.2	±0.2	±0.1	±0.1	±0.1
Urine volume, ml/24 h							
Mean	49	85	92	102	139	193	252
S.D.	±17	±48	±38	±43	±43	±48	±53
S.E.M.	±5.5	±17	±9	±10	±15	±18	±17

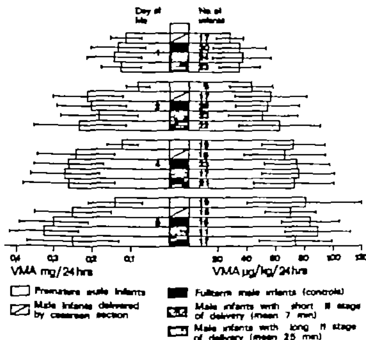


Fig 3 Mean VMA excretion of newborn male infants in different conditions associated with birth (left mg/24 hrs right µg/kg per 24 hrs) Dispersion=1 S D

Children between 1 week and 15 years

Selected hospitalized children 1 week to 24 months of age (Table 5 Fig 2) — These 64 children (115 samples) were divided into three age groups 1) 7—30 days (mean 15 2 days) 2) 1—6 months (mean 2.5 months) and 3) 6—24 months (mean 11.5 months) The mean excretions of VMA in these age groups were 0.35 ± 0 03 0 64 ± 0 07 and 1 08 ± 0 05 mg per 24 hrs respectively and the rise of VMA excretion from one group to another was significant (from group 1 to 2 p < 0.01 from group 2 to 3 p < 0 001)

On the basis of body weight the mean VMA excretions in the three groups were 107 ± 8 132 ± 11 and 108 ± 4 µg/kg per 24 hrs, espectively The middl one of these eadings, i.e., that fo the group 1—6 months old, wa the highest among all the age groups of the whole series of ch ldren between 1 week and 15 years, being ignif icantly greater than the excretions of those 6—24 months and 4—6 6—8 and 12—15 years of age (p<0 05 o p<0 01)

In age groups 1 nd 2 mentioned above the mean VMA content of urine was on nearly the same level (1.5 ± 0 2 and 1 9 ± 0 2 µg/ml per 24 hrs) on the 5th day of life (1.5 µg/ml per 24 hrs), but was signif icantly increased in age group 3 to 3 9 ± 0 4 µg/ml per 24 hrs (from group 2 to 3 p< 0 001).

The mean VMA excretion for all selected hospitalized children from 1 week to 24 months of age was 116 ± 5 µg/kg per 24 hrs, th standard deviation being ± 40 µg/kg per 24 hrs (Table 7) The lower and upper limits of VMA excretion in this series of ch ldren, with ± 2 S D from the mean value were 36 and 196 µg/kg per 24 hrs.

Healthy children between 2 and 15 years (Table 5 Fig 2) — A total of 164 healthy children 2—15 years (84 girls and 80 boys, 188 samples) were divided into six age groups (1—6)

1 2 3 — In children of the age of 2—4 (n=41) 4—6 (n=19) and 6—8 (n=23) years the mean VMA excretion was 1 61 ± 0 06 1.93 ± 0 08 and 2.33 ± 0 08 mg per 24 hrs, respectively Thus the rise in VMA excretion from one group to another was almost linear and was significant (p< 0 001).

The VMA excretions per unit of body weight were 118 ± 4 102 ± 3 and 97 ± 3 µg/kg per 24 hrs in th respective groups and thus showed a very slight decrease with increasing age The mean of 118 µg/kg in the 2—4 year old children was significantly higher than in the following age groups of

children 4—6 and 6—8 years old ($p < 0.01$) and significantly higher than in the preceding age group of 6—24 months old infants ($p < 0.05$)

The mean VMA content of urine remained almost constant 3.6 ± 0.2 3.8 ± 0.3 and 3.6 ± 0.3 µg/ml per 24 hrs, respectively

4 5 6 — In children of the age of 8—10 (n=19) 10—12 (n=19) and 12—15 (n=43) years the total mean excretions of VMA were 2.93 ± 0.13 3.73 ± 0.23 and 4.26 ± 0.18 mg per 24 hrs. The rise from one group to another including also the 6—8 year group was significant with the exception of age group *12—15 years* ($p < 0.05$ or 0.01)

The mean VMA excretions per unit of body weight were 110 ± 5 107 ± 6 and 92 ± 4 µg/kg per 24 hrs. The *first* value 110 µg for children of 8—10 years, was significantly higher than that for children aged 6—8 years ($p < 0.05$) and also significantly higher than that for children 12—15 years of age ($p < 0.01$)

The VMA content of urine increased in these groups from 4.1 ± 0.3 to 5.1 ± 0.3 µg/ml per 24 hrs.

1—6 — The mean VMA excretion per unit of body weight for all healthy children between 2 and 15 years of age was 105 ± 2 µg/kg per 24 hrs, the standard deviation being ± 22 µg/kg per 24 hrs (Table 7) The "normal" range of VMA excretion in this age period, with ± 2 S D from the mean value was 61—149 µg/kg per 24 hrs.

All children between 1 week and 15 years. — When all series of both "selected" and healthy children between 1 week and 15 years of age were combined (n=228) the mean VMA excretion per kg of body weight was 107 ± 3 µg/kg per 24 hrs, standard deviation being ± 45 µg/kg per 24 hrs (Table 7) The upper limit of the VMA excretion with ± 2 S D from the mean value was 197 and the lower limit 17 µg/kg per 24 hrs.

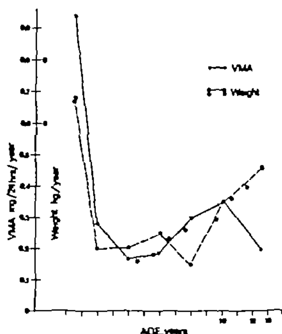


Fig 4 Mean annual increment of VMA excretion (mg/24 hrs per year) and of weight (kg per year) in children in normal conditions series. Open circles show the weight increments of Finnish children according to ... of T ... (90...) and Bäckström Järvinen (16)

Annual Increment

To calculate the annual increment in the mean daily VMA excretion (mg/24 hrs per year) of the children in the normal series (including the selected hospitalized children 1 week to 24 months of age) and the annual increment in the mean body weight of the children (kg/year) the excretion and body weight increments from one age group to another were divided by the time period between the mean ages of each two groups. The curves obtained are presented in Fig 4. The starting values in the first year are the means of infants 5 days of age

Table 7 *Mean urinary VMA excretion (µg/kg/24 hrs) of children in certain age group combinations of normal conditions series*

Age group combination	No. of children	Mean	S D	S.E.M.
7 ds— 6 mos	37	120	±43	±7
7 ds—24 mos	64	116	±40	±5
7 ds—15 yrs	228	107	±45	±3
6 mos—15 yrs	*191*	*104*	*±42*	*±3*
2 yrs —15 yrs	164	105	±22	±2

It is seen from the figur that the annual increment in the mean daily VMA excretion of hildren in the normal series varied con siderably It dropped abruptly from a maximum increment of 0 94 mg d ring the first year of life to a m n mum ncrement of 0.17 mg per year between the mean ages of 3 and 5 years. Another peak, 0 35 mg/24 hrs per year w reached at about the age of 10 years, w th aga n a sharp de crease between the mean ages of 11 and 14

The curve of this annual increment runs on the whole, parallel to the curve for annual increment of body weight up to th age of about 10 years, but while the weight increment curve continues to rise the in crement curve for the mean da ly VMA ex cretion falls after this ge

Correlation to age, body weight and urine volume

In the calculations of correlations between the mean values in the different ge groups 24 hour urinary VMA excretions of children between 2 and 15 years showed a good correlation to age ($r=0\ 99$ $p < 0\ 001$) and as a function of age also to body weight ($r=0\ 98$ $p < 0\ 001$) and to the urine volume ($r=0\ 97$ $p < 0.001$) (cf Fig 2)

The correlation of the da ly VMA excretion to the correspond ng urine volumes was studied by adding up from all the age groups the individual VMA excretions (μg/kg per 24 hr) in those urine volumes that in relation to the mean olume of th respective age group were large (≥ mean +1 S D) or small (≤ mean −1 S D) The mean excretion of VMA in the former group of large urin olumes was 109 ± 4 6 μg/kg per 24 hrs (mean urine volume 1180 ml/24 hrs) and in the latter group of small volumes t was 87 ± 3 6 μg/kg per 24 hrs (mean urine volume 420 ml/24 hrs) The difference wa sign ficant ($p < 0\ 01$)

Sex difference

A significant though mall sex difference in the VMA excretion per kg of body weight was found onl between the bo and girl 2—4 years of age (127 and 112 μg/kg per 4 h respectively $p < 0\ 05$ Table 8) The total series of children 2—15 years of age showed no statistically significant sex differ ence

Diurnal rhythm

F g 5 show th d rnal rh thm of urinary VMA excretion in children during periods of 8 hou Dur ng the forenoon afternoon and night 19 children aged 5—15 years had mea VMA exc etions of 1 23 ± 0 12 1 34 ± 0 09 and 0 95 ± 0 09 mg/8 hrs re pectivel The mean nocturnal VMA ex retion wa sign ficantly lower than the mean excretion in the afternoon ($p < 0\ 05$). The d fference between the forenoon and night excretions was not signif cant

Day and night excretions were also studied in 12 hou periods n four group (Table 9) onl two of which (groups A and D) showed a significant difference between the da and night excretions ($p < 0.01$).

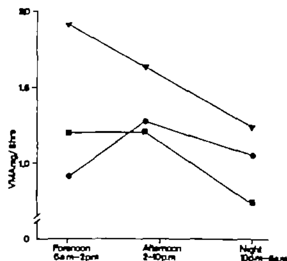


Fig Diurnal h hm of mean VMA excretion in different child groups during 8 hour per ods Symbols ● hildren at home (n=7 between 2 5 nd 15 years of age ▼ juvenile form school boy (n=5) between 12 and 14 years ■ patients (n=7 at hildren psychiatric uni betw en 7 and 14 years

Table 8 *Mean urinary VMA excretion (µg/kg/24 hrs) of boys and girls in different age groups between 2 and 15 years of age*

Sex	Age, years Range	Mean	Body weight, kg	No. of children	Urine volume, ml/24 h Mean	VMA excretion µg/kg/24 h Mean	S.E.M.	p
Boys	2—4	2.8	13.8	17	451	127	±4.1	<0.05
Girls	„	2.9	13.7	24	496	112	±5.0	
Boys	4—8	5.8	21.7	22	599	102	±3.4	>0.05
Girls	„	5.8	21.5	20	665	97	±2.3	
Boys	8—12	10.0	31.0	20	867	113	±5.2	>0.05
Girls		9.8	31.4	19	787	102	±5.7	
Boys	12—15	13.7	45.2	21	976	99	±7.3	>0.05
Girls	„	13.9	49.1	22	917	85	±3.6	

Boys/Girls p >0.05

Table 9 *Diurnal rhythm (night/day) of mean urinary VMA excretion (mg/12 hrs) in healthy children in 12 hour periods (7 a.m.—7 p.m., 7 p.m.—7 a.m.) in different age groups and conditions*

Group	Age, years	Time of urine collection	Mean VMA night/day mg/12 h	p
A Day-nursery children (n=25)	2—4	Nov 1963	0.6/0.8	<0.01
B Summer colony children (n=25)	4—8	July 1963	1.1/1.2	>0.05
Juvenile reform school boys				
C Kulho (n=10)	13—15	Sept. 1963	1.8/2.1	>0.05
D Laust (n=10)	13—15	May 1964	1.1/1.9	<0.01

Table 10 *Mean urinary VMA excretion (mg/24 hrs µg/kg/24 hrs) and mean urine volume (ml/24 hrs) of juvenile reform school boys in summer and winter*

	No. of boys	VMA excretion/24 h µg/kg Mean		mg Mean		Urine volume/24 h ml Mean	
Summer	13	3.5	p<0.01	64	p<0.05	1487	p<0.05
Winter	11	4.2		98		2037	

Other normal conditions studied

The VMA excretion was studied in a small group of reform school boys (Table 10) during a 24 hour period in early summer and in midwinter

Details of this study ere as follow Summe group Mean age 14 years (13), eight 53 kg outdo r tem perature at 2 p.m. on day of urine collection in Ma 1964 was 21°C. Winter group Mea age 12 8 ears (n=11) eight 44 kg outdoor temperatur at 2 p m on day of urine collection in J nuary 1965 was 3 C, and on the preceding day — 21°C.

The winter group had significantly higher mean VMA excretions than the summer group both as to the total daily amount ($p<0\ 01$) and the amount per kg of body weight ($p<05$) The mean urine olume also wa significantly higher in the winter group than in the summer group ($p<0\ 01$)

Urine volume

The urine volumes in the different age groups between birth and 15 years in the normal series are presented in Table 5

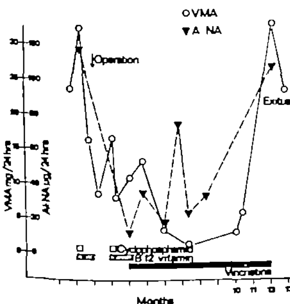


Fig 6 Excretion of VMA mg/24 hrs) and combined A and NA (µg/24 hrs) of 3-year old boy with neuroblastoma Note the effec of treatment

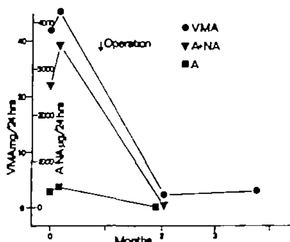


Fig 7 Excretion of VMA mg/24 hrs A and NA (µg/ 4 hr of 7 ar old girl th pheochromocytoma Not the effe of ope ation

URINARY EXCRETION OF VANIL MANDELIC ACID IN CERTAIN PATHOLOGICAL CONDITIONS

Observed increased excretion

Neuroblastoma and pheochromocytoma

Case 1 (Fig 6) A 2 year-old boy was found to ha e the typical clinical picture of *neuroblastoma* The diagnosis was confirmed by the h stological examination of a tumor removed from the retroperitoneal space The urinary VMA excretion was elevated up to 32 5 mg per 24 hrs. Operation nd treatment with cytostatics was followed by clinical recovery from symptoms and return of the VMA excretion to 1 2 mg per 24 hrs, which is within the normal range. In a few months this excretion, however increased again and simultaneously symptoms reappeared as sign of recidivation of the disease

Case 2 (Fig 7) A 7 year-old girl with a history of episodes of sweating and loss of body weight had an elevated blood pressure a positive phentolamine test and VMA ex cretions up to 35 4 mg per 24 hrs. After removal of a tumor in the right adrenal gland the patient became symptomless and the VMA excretion fell to 2.3 mg per 24 hrs. The path ologist s examination confirmed the diagnosis of *pheochromocytoma.*

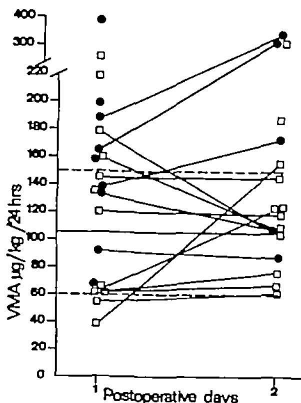


Fig 8 Individual VMA excretions (µg/kg per hrs) on the 1st nd 2nd postoperat days al ious surgical measures, ompared ith the mean ± S D ( ) of healthy hildren 2—15 years of a Symbol ● heart or thoracic operation, □ other operati

Table 11 *Individual urinary VMA excretions (µg/kg/24 hrs) of operated patients 1st and 2nd postoperative days*

Case no.	Diagnosis and/or operation	Age	VMA excretion, µg/kg/24 h	
			1 t day	2nd day
1	Cong heart disease; pulmonary emphysema; lobectomy	3 mos	333	—
2	U ethral stricture; dilatation	3	121	119
3	Hydronephrosis plastic repair	9	145	147
4	H rschsprung disease colostomy	1 yr	—	316
5	Closure of V.S.D)	4 yrs	68	—
6	Closure of V.S.D)	5	137	—
7	Closure of V.S.D)	5	165	317
8	Closure of V.S.D)	6	134	103
9	Aortic resection)	6	188	347
10	Inguinal hernia; herniotomy	7	178	103
11	Pulmonar valvulotomy	7	63	124
12	Hydronephrosis; nephrostomy	7	39	157
13	Appendectomy	8	160	109
14	B liary cirrhosis splenectomy	9	—	125
15	Appendectomy	9	—	189
16	Orchidopexy	10	219	—
17	Hypospadia, urethroplasty	11	63	67
18	Appendectomy	11	62	77
19	Closure of V.S D.)	11	138	173
20	Skin grafting	12	35	61
21	Appendectomy	13	136	—
22	Wound closure	14	259	—
23	V lvulotomy; closure f A.S D)	14	92	89
24	Aortic resection)	14	199	—

) Open heart surgery — Nos. 5—24: Mean 152 (1st day), 146 (2nd day); S.E.M. ±15 (1st day), ±23 (2nd day)

Surgical operations

The mean VMA excretions of the 1st and 2nd postoperati e davs of 4 ch ld en under 4 years of age were 388 190 146 and 316 µg/kg/24 hrs, respectively

In 20 children 4 to 14 years of age the mean VMA excretion was 13 ± 15 on the 1st and 146 ± 23 µg/kg per 24 hrs on the 2nd postoperative day Thus the mean ex cretion did not exceed significantly the corre sponding excretion of healthy children of the same age (T ble 11 F g 8)

When all the patients in the surgical group were divided nt max mum and minimum excret on subgroups ord ng to th size of the postoperat e VMA excretion per kg of bod w ight n e ther the 1st o nd postoper tiv d y th fo mer ubgro p (12 ch ldren) had mean VMA excretion of 24 (range 157—388) µg/kg in 24 hrs and the latter) hild en o l 109 (range 61—157 µg/kg in 4 hrs The latter alue was the same a n th ontr l series but the former was clea ly nc eased

Table 12. *Individual urinary UMA excretions (; g/kg/24 hrs) of patients with congenital heart disease with or without heart failure*

Case no.	Diagnosis	Age	VMA excretion, µg kg 24 h Mean)	Respiration rate/mi	Heart rate/min	Enlarged heart	Edema	Cy nosis	Digitalis	Heart failure
1	Cong heart disease	1 day	45 (2)	80	150	+	+	+	+	+
2	Pulmonic stenosis	2 ds	63 (2)	40	150	—	—	—	—	—
3	V.S.D. pseudotruncus Down s syndr	7	63 (2)	45	150	—	—	+	+	C
4	A.S.D ; V.S.D	10	49 (2)	60	140	+	+	+	+	+
4	— — — —	20	116 (2)	85	160	+	+	+	+	+
5	P.D.A.; dextrocardia	23	147 (2)	50	150	—	—	+	+	+
5	— — — —	2 mos	85 (2)	40	150	—	—	+	+	C
5 b	— — — —	3¹/	142 (2)	45	160	—	—	+	+	+
6	Endocardial sclerosis aortic stenosis	3	219 (2)	60	140	+	—	—	+	+
6	Endocardial sclerosis; aorti stenosis	4	94 (2)	50	120	+	—	—	+	C
7	Cong heart disease; pulmonary emphysema	3	274 (2)	60	140	+	±	±	+	+
8	V.S.D	5	193 (2)	50	140	+	+	±	+	+
8	— —	7	531 (2)	63	145	+	+	—	+	+
9	A.S.D.	5	156 (1)	65	150	+	—	+	+	+
10	V.S.D	9	117 (2)	40	110	±	—	—	—	—
11	V.S.D	11	123 (1)	40	130	+	—	—	+	C
12	Fallot trilogy	3 yrs	118 (1)	N	85	—	—	—	—	—
13	A.S.D	4	126 (1)	N	90	+	—	—	—	—
14	P.D.A.	6	89 (1)	N	90	+	—	—	—	—
15	V.S.D ; aortic stenosis	6	374 (1)	N	85	+	—	—	+	C
16	A.S.D	12	155 (2)	N	70	+	—	—	—	—
17	Myocardosis	13	65 (1)	N	90	+	+	±	+	+
18	V.S.D.; hypothyreoidism	14	90 (2)	N	80	+	—	—	+	C
19	Fallot' pentalogy	15	111 (1)	N	70	+	—	—	—	—
20	V.S.D.; aortic stenosis	15	69 (2)	N	60	+	—	—	—	—

A.S.D — Atrial septal defect
V.S.D — Ventricular septal defect
P.D.A. — Patent ductus arteriosus
N — Normal
C — Compensated heart failur
4, 4 etc. — Same patient at different ages
) Number f days of urine collection stated in parentheses

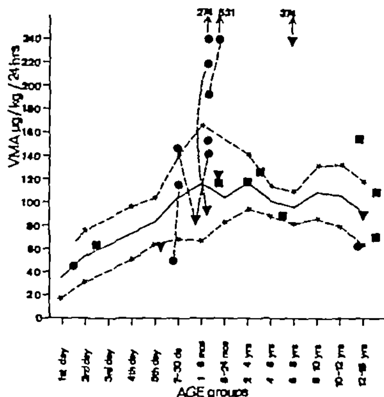


Fig 9 Individual mean VMA excretions (µg/kg per 24 hrs) in congenital heart diseases with heart failure (●), with compensated heart failure (▼) and without heart failure (■), compared with the mean ± S D (—) for the different age groups of the normal conditions series ● — — ● VMA excretion values of individual patients determined at different times.

Congenital heart disease with or without heart failure

In infants (mean age ca 3 months 11 urine samples of 7 infants) suffering from heart failure the mean VMA excretion per kg of body weight 187 ± 44 µg was higher than the mean excretion in the control group nearest in age (from 1 week to 6 months 120 ± 7 µg/kg per 24 hrs) However the difference of the means was not significant. The urinary VMA excretions of children with congenital heart disease without heart failure or with compensated heart failure (14 samples) were on the whole on the same level as in the normal series (Table 12 Fig 9)

Febrile infections

The mean VMA excretion per kg of body weight, 154 ± 16 µg of 8 children 5 months to 8 years of age whose mean body temperature exceeded 39 0°C was significantly higher than that in the control series of 6 months to 15 years (104 ± 3 µg/kg per 24 hrs) which is the best comparable age group ($p < 0.01$) There was a significant positive correlation between the VMA excretion and the body temperature ($r = 0.55$ $p < 0.01$) (Fig 10)

Acute bronchial asthma

During the first 24 hour period of treatment the mean VMA excretion of 152 ± 16 µg/kg per 24 hrs of 7 children 2—14 years of age with acute bronchial asthma was significantly greater ($p < 0.01$) than that in the normal series, but already on the second hospital day it was, at 117 µg/kg per 24 hrs ($n=6$) within normal limits and only slightly above the mean of the controls. On the third day the VMA excretion, 61 µg/kg per 24 hrs ($n = 4$) was below this mean.

During the first 8 hours of hospitalization the mean VMA excretion per hour was 7 0 µg/kg in the second 8 hour period 5 7 µg and in the third 5.8 µg — In the whole first 24 hour period the VMA excretion per hour was 6 4 µg/kg ($n=7$) in the second 4 9 µg ($n=6$) and in the third 2.5 µg ($n=4$).

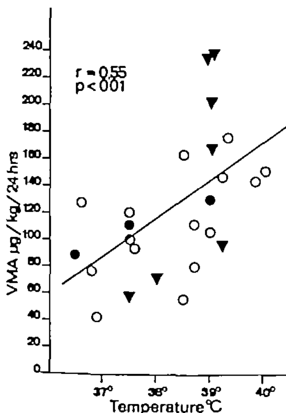


Fig. 10. Relationship between VMA excretion (µg/kg per 24 hrs) and body temperature (°C). O: 9 children with febrile diseases. 25 urinary VMA determinations were made on successive days and the mean axillar or rectal measurements of body temperature were noted on the same day. Symbol: O measles, ▼ purulent meningitis, ● acute pyelonephritis.

Exchange transfusion in hemolytic disease of the newborn

Eight newborn infants with hemolytic disease who had been given an exchange transfusion on their first day of life had on the second day a urinary VMA excretion of 90 ± 14 µg/kg per 24 hrs. This was slightly but significantly higher ($p < 0.05$) than the corresponding VMA excretion of the normal newborn (54 µg/kg per 24 hrs). However the VMA content of the urine in this group was 4.9 µg/ml per 24 hrs, i.e. the same as in controls (4.74 µg/ml per 24 hrs), but the mean urine volume, 78 ml per 24 hrs, was about 50 % greater than that of the controls.

Observed decreased excretion

The lowest individual VMA excretion, 4 µg/kg per 24 hrs (mean of 7 samples) was found in a 15 year old patient with *chorea minor*.

Two children with *renal disease* having increased blood urea nitrogen levels of 122 and 76 mg/100 ml and diminished urine volumes, had clearly decreased VMA excretions, 23 and 26 µg/kg per 24 hrs. On the other hand, three other children with renal disease whose blood urea nitrogen values were in the range 68—78 mg/100 ml but the urine volumes were normal or large had VMA excretions within the normal limits, i.e. 70—116 µg/kg per 24 hrs.

A 9 year-old girl with *paraplegia of the lower extremities* due to a tumor of the lumbar spinal cord had a clearly decreased VMA excretion, 32 µg/kg per 24 hrs.

Clearly decreased VMA excretions, 33 µg/kg per 24 hrs were seen in two patients with *pyloric stenosis*. The mean VMA excretion in the whole group with this disease (n=9, mean age 1.3 months) also was significantly lower (73 ± 7 µg/kg per 24 hrs) than that in the 2.5 months mean age group of the "normal" control series ($p < 0.01$).

Decreased VMA excretions, 53—58 µg/kg per 24 hrs, were observed in three among four children with *hepatic disease* and with GOT readings in the range 65—400 RFU/ml and slightly increased serum bilirubin levels.

One of two children with severe *heart failure* had a decreased VMA excretion of 49 µg/kg per 24 hrs and the other 63 µg/kg per 24 hrs, i.e. at the lower limit of normal (Nos. 4 and 17, Table 12).

Observed normal excretion

Respiratory distress syndrome of the newborn

In 13 newborn infants (1—5 days old) with a moderate or mild RDS the mean VMA excretion per kg of weight was on the same level as in the control series on the 1st—5th days of life (Table 13).

Hormonal and metabolic diseases

In eighteen children with *diabetes mellitus* the mean urinary VMA excretion of 101 ± 3

Table 13 *Mean urinary VMA excretion during first 5 postnatal days (μg/kg/24 h; means of 4—8 urine samples on different days) of 13 newborn infants with respiratory distress syndrome compared with respective controls*

Age, days	No. of urine samples	Resp. rate/min. Mean	VMA μg/kg/24 h RDS Mean	Controls Range	Controls Mean
1	4	95	33	4—46	35
2	6	83	64	32—107	54
3	6	7	75	19—152	
4	8	63	6[illegible]	15—106	75
5	6	61	92	39—13	84

Table 14 *Individual urinary VMA excretion (μg/kg/24 hrs) of patients with endocrinological disorders*

Case no	Diagnosis	Age years	Sex	VMA excretion, μg/kg/24 h Mean	Body weight, kg
1	Idiopathic hypoglycemia	1	m	1[illegible]0 (2)	10.5
2	Precocious puberty	1	f	102 (2)	15.5
3	Nanism	4	f	248 (1)	10.4
4	Hyperthyroidism	4	m	112 (2)	13.5
4 a	Hyperthyroidism)	4	m	77 (2)	13.3
5	Obesity	5	m	40 (1)	40.0
6		6	f	92 (2)	40.0
7	Adreno-genital syndrome	8	f	55 (1)	31.9
8	Obesity	8	f	88 (*)	33.0
9	Struma (euthyr.)	9	f	92 (1)	34.0
10	Addison's disease**)	9	m	69 (1)	29.0
11	Hyperthyroidism	10	m	122 (1)	27.0
12		10	f	203 (1)	25.0
13		12	f	86 (1)	40.0
14	Hyperthyroidism; acute infection	12	f	106 (1)	33.0
15	Nervous anorexia; secondary hypothyroidism **)	13	m	139 (1)	31.0
16	Nanism	13	f	75 (2)	53.0
17		14	f	6[illegible] (1)	34.0
18	Hyperthyroidism	14	f	100 (1)	51.0
18 a	Hyperthyroidism****)	14	f	97 (1)	51.5

Number of days of urine collection stated in parantheses

*) After 3 days treatment with Thyroid Gland® daily dose 2×0.06

) Hydrocortisone treatment, 2×20 mg daily

**) After one week treatment with Thyroid Gland® daily dose 2×0.06

**) After 2—3 months treatment with carbimazol; PBI 20 γ / → 7 γ /

kg per 24 hrs did not differ significantly n the excretion in the normal series of dren aged 2—15 years. In this group no ificant correlation was found between the IA excretion per kg of body weight and glucose excretion per 24 hrs (r= +32 > 0.05) The duration of the disease or the sence of ketoacidosis seemed to ha e no ct on the VMA excretion in the examined up which was small, howev er

Eighteen children with various *other mal or metabolic diseases* are presented Table 14 The VMA excretions calculated r kg of body weight were on the normal el in these children with a few individual ceptions (Nos. 3 5 7 and 1)

her diseases

In a small group of neurological diseases th the exception of the child with cho ea min n t r l al and p hiatric or ps ch c iat l e s and in progres ive muscular dystroph as well as n ne phrosis th VMA excretion seems to be generally normal in the light of the cases studied.

Sixty seven h ld p tients of different ages (not cluded in the bove mentioned groups of ch ld en most of whom had been hosp talized bec s t pr longed mino ailment pag 5 lse had VMA ex ret on within the limits of normal.

1 F hildren th erebral palsy six epileptic children one 12 ear old patient with Recklinghausen disease d one non-febrile child th meningitis

2 One child th autistic infantile psychosis, two th emotional instability and two th neurodystonia

3 Three hildren

4 One child th ongenital nephrosis and six children h lipoid nephrosis

DISCUSSION

URINARY EXCRETION OF VANIL MANDELIC ACID IN NORMAL CONDITIONS

Newborn infants

In the present series of *fullterm newborn* male infants the low *mean excretion of VMA* on the first day of life 0 13 mg/24 hrs and 55 μg/kg per 24 hrs is worth of attention. These excretion values were doubled, however as early as on the 4th day and tripled at about the age of 2 weeks, when the latter excretion had reached the mean excretion *level of the* entire childhood Results comparable to these have been presented by Zeisel (332) and Boehm & O Brien (23) However greatly diverging findings have also been reported by Nicolo poulos *et al* (191) according to which the VMA excretions in a relatively small series of 11—9 fullterm newborn infants were higher on the first day of life than on the 15th day

It seems probable that the low VMA excretion *on the first few days of life* observed in the present study is associated mainly with the poor neonatal renal function and low excretory capacity This idea is supported by the ob servation by Glowinski (91) that the newborn rat, in spite of its ability to metabolize radio active NA administered i v is hardly able to excrete its metabolites before the 11th day of life Theoretically a limiting factor in the production of VMA might be a relative deficiency of MAO and COMT which evidently is the fact in the newborn organism (27 91)

On the other hand as observed earlier by v Studnitz (292) the *mean VMA content of* urine decreased significantly between the 1st and 5th day of life from 4 9 μg/ml to 1 5 μg/ml per 24 hrs as a result of the greater increase in the urine volume than in the VMA excretion (former 6 6 fold latter 3 4 fold)

In the present study there was no difference in the urinary VMA excretion between the newborn infant groups *delivered by the cesarean section and the vaginal route* Evidence of the different stress effects in newborn infants as a result of delivery by cesarean section and by the vaginal route are, however the greater catecholamine content of the initial voided urine (118) and the greater NA excretion on the 3rd day of life (39) by the latter than by the former infants. The greater 17 OHCS content in plasma observed by Migeon (183) and the higher cortisol production rate found by Kenny *et al.* (145) in infants born by the vaginal route than in those delivered by cesarean section agree with the above findings.

According to Fiorino (71) in three cases of rapid delivery and an especially short second stage the A and NA contents in the maternal and umbilical cord blood were identical, while in 17 deliveries of normal duration the A and NA contents in cord blood were two-fold as compared with the maternal value. However in the present study the *duration of the second stage of delivery* had no significant effect on the VMA excretion (Fig.5).

The *mean VMA excretions per kg of body weight of the premature infants* (Table 6 Fig 3) were on the first days of life and at the age of about 2 weeks similar to the mean excretions of the corresponding controls (Table 5) Cession Fossion *et al.* (48) obtained a mean VMA excretion of 151 μg/kg per 24 hrs in 12 premature infants. This value was similar to the excretion of 156 μg/kg per 24 hrs *obtained in the present study for premature* infants slightly under 1 month of age, but which in turn was significantly higher ($p < 0.01$) than those in groups of two weeks mean age of both prematures and "normal" control infants.

The relatively abundant mean urine out put on the 2nd day of life of the premature newborn infants and their significantly lower mean urinary VMA content as compared to the fullterm newborn were apparently a consequence of their larger amount of total body fluid (75)

Among the other very few studies of VMA excretion of premature newborn Brunjes *et al.* (27) have reported that the MA+MNA/VMA ratio on the first day of life was higher than those of fullterm infants and adults. To an abnormality in the catecholamine metabolism of prematures point also the findings that premature infants had on the 15th day of life greatly elevated dopamine and VMA excretions as compared to fullterm infants (190, 191). These VMA excretion values (page 13) differ, however, clearly from those in the present study. In the study on Nicolopoulos *et al.* (190) the A excretion per kg of body weight by premature infants was on the 1st and 15th days of life the same as that by fullterm infants and the NA excretion was significantly lower than that by the latter. These results differ on the other hand markedly from the findings of Cession-Fossion *et al.* (43) according to which the A and NA excretions per weight unit of premature infant (age not mentioned) were 3—4 times as high as those by the fullterm, and the total excretion was at the level of children 2—4 years of age.

Due to the small number of VMA studies of premature infants and the partly conflicting results a final answer cannot as yet be given concerning the relationships of the A and NA metabolism and the VMA excretion of premature infants, and this subject therefore calls for futher research.

Children between 1 week and 15 years

The increase in the *mean 24-hour VMA excretion* with increasing age during the entire childhood (Fig. 2) as well as its significant correlation to age is in agreement with many earlier studies (174, 181, 304), but the fluctuation appearing in the present study in the annual increments of the daily VMA excretion (Fig. 4) has not been reported in any of the previous studies. The clear parallelism up to prepuberty of the curves for the annual increments of mean daily VMA excretion and of mean body weight and their greatly diverging course after this age is of interest. In contrast to the continuing rise in the annual increment of body weight, the increment in VMA excretion decreased abruptly after about the age of 10 years.

If we accept the concept that the VMA excreted in the urine is a measure of mainly the NA synthesis (331), *the annual increment in the VMA excretion of a growing child might consequently reflect an increase both in the quantity of noradrenergic neurones and in their ability to synthesize NA.* The picture thus obtained of the quantitative aspects of the development of the noradrenergic nervous system is supported by the investigation of Scammon (263), which revealed that after the 10th year of life there is very little increase in the total amount of nervous tissue, whereas the period of greatest increase of body weight still lies ahead. A clinically interesting question is the significance of this possible disproportion between physical growth and growth of the noradrenergic neurones of the sympathetic nervous system in the lability phenomena associated with the age of puberty.

It was already stated above that the *VMA excretion per kg of body weight* increased rapidly during the first days of life and at the age of about 2 weeks reached the mean level of the entire childhood (Table 5, Fig. 2). However, partly significant differences could be seen in the VMA excretion between the different age groups and small excretion peaks were demonstrated in the age groups of 1—6 months, 2—4 years and 8—10 years. — With the exception of early infancy the last mentioned rises in the VMA excretion per body weight unit find no support in previous studies. The question still remains unanswered as to what extent these excretion peaks possibly reflect, for instance, the increased physical acitivity of corresponding age periods or the activity and readiness of the sympathetic nervous system to respond, or some other circumstance.

As a whole from early infancy onward the VMA excretion per kg of body weight had a slight downward trend, supporting the earlier findings of Zeisel (332), Cession-Fossion *et al.* (43) and Voorhess (311). A good linear correlation was found, however, in the present study between the 24 hour mean VMA excretion and the mean body weight in the different age groups, as has also been demonstrated earlier (181). The amounts of VMA excretion of infants obtained by Cession-Fossion *et al.* (43) and Voorhess (311) were similar to ours, whereas Zeisel's (332) result (60—83 μg/kg per 24 hrs in infants 2—12 months old) were lower. For older children (1—15 years) other authors (Table 2) have reported VMA excretion values of about 90—

60 μg/kg per 24 hrs (Zelsel obtained only 46—52 μg/kg per 24 hrs in children 2—15 years of age) i.e., in part clearly less than in the present study

The differences referred to above in the results reported in the literature can probably be explained not only by differences in the methods used but also by factors related to the research conditions which might have an effect on the VMA excretion, for instance the climate

"Normal" range of VMA excretion. — The range with ± 2 S D calculated from the mean for all healthy children between 2 and 15 years of age was 61—149 (rounded out to 60—150) μg/kg per 24 hrs (cf Table 7) Since inside this age period considerable variations occurred as well in the mean VMA excretion as in the dispersion of the individual values the results presented in Table 5 naturally give a more accurate picture of the VMA excretion characteristic of each age group *These range values can be recommended for practical clinical use as guide values for Finnish children over 2 years of age at least when the determinations are made by the Pisano et al (221) method or its modifications and the results are corrected for recovery*

The results for selected hospitalized children of 6—24 months (Table 5) show that the *above VMA excretion results for healthy children of 2—15 years can be applied also to age of 6—24 months* without any error worth mentioning In the age group of 1—6 months the mean VMA excretion per kg of body weight was 152 μg/kg per 24 hrs, which was the highest excretion of all age groups in the present study Also the dispersion of the VMA excretion was widest in this group the standard deviation being ± 50 μg/kg per 24 hrs (range values with ± 2 S D = 52—252 μg/kg per 24 hrs) In the age group of 7—30 days the mean VMA excretion was 107 μg/kg per 24 hrs, or the same as that for the entire childhood but the dispersion of the excretions in also this age group was considerable, the standard deviation being ± 36 μg/kg per 24 hrs (range values with ± 2 S D = 35—179 μg/kg per 24 hrs)

It is difficult to say if the ailments of these "selected" children or their hospitalization has had an effect on the results obtained but this possibility does naturally exist. As also the VMA excretions per kg of body weight reported in earlier studies (45 311 332) have been higher for infants than in later childhood the above mentioned results for selected hospitalized children can be considered to be at least directive *The value of 200 μg/kg per 24 hrs can thus be regarded as a rough upper limit for the VMA excretion of children under 6 months of age*

Concerning the lower limit of normal VMA excretion, examination of the individual low VMA excretions in the age groups of 7—30 days and 1—6 months showed that only two children had a VMA excretion below 60 μg/kg per 24 hrs (45 and 59 μg/kg per 24 hrs respectively) For this reason, also for these children under 6 months 60 μg/kg per 24 hrs can be considered a practical lower limit

But why express the amount of VMA excretion on the basis of body weight? — In adults v Studnitz (292) demonstrated that the VMA excretion expressed on the basis of the VMA/creatinine ratio gives a less accurate value than determination per 24 hour volume of urine It also has been shown that the excretion of endogenous creatinine is accelerated in relation to body weight from the end of age 1 years onwards (127 286) for which reason in the study of e g Gitlow *et al.* (84) the values of mean VMA excretion expressed in μg/mg creatinine in children under 1 year was 4 to 5 fold that at puberty So in case the intention is to study the relative amount of VMA excretion in different age periods of childhood it is apparent that for this purpose the calculation of VMA excretion on the basis of creatinine output is unsatisfactory to say the least. Concerning the expressing of the excretion on body weight basis, it was seen above that the curve for annual increment in the mean total 24 hour VMA excretion resembles fairly closely the curve describing the annual body weight increment up to the age of about 10 years (Fig 4) In other words, the amount of basal daily VMA excretion of a growing child increases during these years in proportion to body weight. Thus it appears that *up to prepuberty age the VMA excretion calculated per weight unit is a practical and evidently also the most reliable manner of expressing the relative amount of VMA excretion in a child of normal weight*

The *mean content of urinary VMA* exhibited marked variations as functions of age and physical development of the children (Table 5 Fig 2) The fact that the urinary VMA

content remained at this low level (about 1 5 µg/ml per 24 hrs) over the first months of life — the period of the most active VMA excretion — is doubtlessly due to the deficient urine concentrating power of the kidneys at this age The physiological improvement in the renal concentration capacity with age is reflected already in infants of 6—24 (mean 11.5) months in the over twofold VMA content as compared to the above figure. The urinary VMA content continued to show a slight upward trend, up to 5.1 µg/ml per 24 hrs, in the groups of older children. This is very close to the values of the adult patients of v Studnitz (292) and Petrášek & Dubovský (213)

The *urine volume* increased more rapidly than the VMA excretion in the neonatal period (Table 5 Fig 2) Later in 2—15 year-olds, a positive correlation as a function of age was evident between the 24 hour urine volume and VMA excretion as calculated from the mean values of each age group This significant correlation as well as that noted between the increases in VMA excretion and body weight with age are merely indications of parallel physiological phenomena in the growing and developing child.

In earlier studies in ad lts no correlation was found between the VMA excretions and the 24 hour urine volumes (213 267 292) Neither did Sunderman (300) find any correlation in cases where the urine volumes were in the range 800—3600 ml/24 hrs, whereas in connection with lower urine volumes, 400—800 ml/24 hrs, the VMA excretions were signif icantly lower This fits in well with the finding in the present study in which cases of ery large o small urine olumes showed a certain degree of correlation between the in dividual urine volumes and the corresponding VMA excretions.

Many reasons may be presented for the above described dependence of VMA excretion on the urine volume in th cases of extreme volumes one of them may be slight un noticed inaccuracy n the collection of th urine even though special attent on was paid to its careful performance The ingestion of coffee, due to its simultaneou diuretic nd VMA excretion promoting effects (334) may also contribute to the correlation between VMA excretion and large urine vol mes. In the present work, however this p obably had ery l ttle effect on the results, for alt ough no dietary restrictions were imposed, ch ildren generally dri k very l ttle coffee

Anot er notewo thy easo fo th x latu might be that ph sical nd possibly also meta bolic activity of child en ma fl nc both the VMA and the u inary excreti in the same direction A certa n theoretical ba is for this ggestion i p o ded b the f hat the osmolar ex t ne depend l on th t k f p tei 1 7 hi h la evidently g ter h f ph all acti e chil ilha le n n

Sex diff ence in VMA excretion — N significant diff enc th mea VMA cretion w oted between bo nd g l the total series b tw en nd 15 of age studied th pe t This in gree ent with the earl e studies by Terslew 304 Matsaniotis *et al* 181 and also M K ndrick & Edward 1 4 f r children 1—11 9 ears of age wherea in the lder group aged 12—15 9 years of the last mentioned stud there was a notabl d fference between the sexes. Contrary to this again, n the youngest age group of the p sent tudy namely in children 2—4 years of age the mean daily VMA excretion was slightly higher in boys than in girls ($p<0 0$) It is difficult to find an ex planation for th difference. The possibility of incomplete urine collection f om girls is also excluded since the daily mean urine volume of girls was even lightly larger than that of boys (491 and 451 ml/24 hrs, re spectively)

Diurnal rhythm of VMA excretion. — It has been observed that the VMA excretion of adults (page 17) a well a that of children (108 174) has a diurnal rhythm, the excretion being greater during daytime activity than during night rest. In daytime the maxim m of VMA excretion of adults may occur either in the forenoon o in the afternoon (301 303) ac cording to Pekkarinen *et al.* (210) in soldiers in military service it occurs mostly in the afternoon. — Likew se in those VMA deter minations in the present study which were made in 8 hour periods the mean VMA ex cretion wa significantly ($p<0.05$) lower at night than in the afternoon (Fig 5) As is the case w th ad lts, the peak VMA excretion clearly occurred in a part of the child en in the forenoon and in a part n the afternoon.

Obviously the differences observed in the individual augmentation of the VMA excretion

at different times of the day and night depend in part at least, on conditions prevailing on the day of examination, for instance on the fact how well certain periods of urine collection coincide with periods of maximum activity or rest (sleep) In the present work this is supported by the similarity of the daily rhythm of VMA excretion observed in individuals in the small subgroups whose external conditions were practically the same. Thus 5 out of 7 children living at home had the 8 hour VMA excretion peak in the afternoon and 4 of 5 reform school children had it already in the forenoon (Fig 5) The ratio between the afternoon and night excretions was 1 7 in patients in the children s psychiatric unit (here the 8 hour urine collection periods began at 7 15 and 23 o clock and in the other groups at 6 14 and 22 o clock) while it was only 1 2—1.3 in the two groups mentioned above

A point worthy of consideration in this connection is the possible effect on the daily rhythm of VMA excretion of the season as such or of the great differences in temperature during the cold season to which a person is exposed who works outdoors in daytime and is mainly indoors at night. Since the A and especially the NA excretion is increased by cold (8) this might be reflected in an accentuated diurnal rhythm of VMA excretion in winter Of interest in this connetion might be the observation of a significant 12 hour variation in the children in groups A and D in Table 9 who were examined during the cold or cool season, in contrast to groups B and C examined under summer conditions who showed no significant difference in the day and night excretions of VMA.

Other normal conditions — The higher mean VMA excretion observed in the study made in January as compared with that made in May (Table 10) may possibly be within the limits of biological variation since only one 24 hour VMA excretion represents each of these examination periods, and also the group studied was relatively small Should this not be the case the observation is of some interest and may be explained by a direct elevating effect of a cold winter day on the VMA excretion, by a seasonal variation of VMA excretion, or by both of these Reference to the views relating to the first alternative was made in the preceding section. No earlier studies pointing to a possible seasonal variation in the VMA excretion seem to have be[...] published in the literature However su[...] a possibility is pointed to with respect [...] NA by the observation of Beauvallet et [...] (17) that the NA content in rat brain und[...] identical conditions and temperatures was [...] October fourfold that in June

URINARY EXCRETION OF VANILMANDELIC ACID IN CERTAIN PATHOLOGICAL CONDITIONS

The pathological conditions related to th[...] part of the study have been classified in[...] three groups according to whether the VM[...] excretions were mainly increased, decreased [...] normal. The evaluation of the VMA excretio[...] for this grouping was based on the excretio[...] values per kg of body weight obtained in t[...] children examined in normal conditions. Be[...]cause some of the pathological condition group[...] are rather small, the results obtained are [...] general to be considered orientative only

Increased excretion

Neuroblastoma and pheochromocytoma. — Th[...] considerably elevated VMA excretions of tw[...] patients, one with neuroblastoma and o[...] with pheochromocytoma (up to 32.5 and 35 mg/24 hrs, respectively) and the definite inver[...] correlation of the excretions with the patient[...] clinical state support many earlier observatio[...] on the usefulness of VMA excretion determ[...]nations in the diagnosis of these tumors an[...] in the evaluation of the results of treatment.

Surgical operations. — Postoperative VM[...] excretions within normal limits were reporte[...] by McKendrick & Edwards (174) in 3 childre[...] In adults, however elevated urinary VMA ex[...]cretions after major surgical operations hav[...] been reported by many investigators (195 216 244 299 318).

In 20 children from 4 to 14 years of ag[...] in the present surgical group the mean VM[...] excretions per kg body weight on the 1st an[...] 2nd postoperative days were close to th[...] upper limit of normal but not significantl[...] above those of healthy children 2—15 years old (Table 11) In about half of the total surgical group of 24 children (age 3 months

to 14 years) however the individual VMA excretions were elevated (up to 388 μg/kg per 24 hrs) on either the 1st or the nd postoperative day the remainder had fully normal excretions (Fig 8)

In the evaluation of these results there must be taken into consideration that the patient's disease may be a factor contributing to an increased postoperative VMA excretion So, for instance, a patient with pulmonary emphysema and heart disease in the present series (No. 1 Table 11) had preoperatively an increased VMA excretion of 274 μg/kg per 24 hrs, which rose to 388 μg/kg per 24 hrs on the 1st post operative day after lobectomy This finding supports the report of Zicha *et al* (337) that surgical operation increases the urinary VMA excretion in patients with heart failure indicating that operation may be a powerful stress factor

It is obvious that many factors tend to increase the postoperative VMA excretion In Sturm's (299) series the highest VMA excretions occurred in connection with fatal surgical complications. Furthermore the VMA excretion is influenced by the size and d ration of the surgical measure as noted by Zicha *et al* (336) and Pekkarinen *et al* (195 200) In minor operations the emotional tension also raised the VMA excretion (267 336) It is of interest that heart operations performed with well managed extracorporeal circulation do not, however differ from other heart operations as far as concerns the VMA excretion (308). — Likewise, increased excretion of A and NA into the urine after major thoracic and abdominal surgery has been reported by Halme *et al.* (111) and others.

It appears from the above that an increased VMA excretion in connection with a surgical operation is to be regarded as the result of stress and also as a certain measure of the magnitude of the stress. The circumstance that the mean VMA excretion in the surgical group of children in the present study was within normal limits and that th individual VMA excretions were elevated in only half of the patients suggest that children have a good capacity for adaptation to surgical treatment and that the stress of operation and anesthesia as well as recovery as manifested in the reaction of the sympathetic nervous system and the adrenal glands, possibly is less sever in children than in dults.

Congenital heart disease with or without heart failure — In an earlier study (169) the VMA and MA+MNA excretions of children with severe heart failu were more than twice as high as those of healthy children, while no significant rises were fo nd n the milder ases In the same investigation th excretions f the above metabolites we e normal h ldren affected with organic heart dise se without heart fa l e Th the presen results a er much along the same l nes far as the VMA excretion n he e d se ses of hildren n cerned

According t Lees 6) an [illegible] ex cretion of metabol te f A and NA [illegible] a probably [illegible] ses e states [illegible] Likewise [illegible] creased excret o of VMA ha e been dem onstrated [illegible] in ad lt [illegible] berger & B klen 117 On the other hand Chidsey *et al* 48 found no s gnifica t ise in the excretion of VMA by dult p tients w th heart failure and Pekkarinen & I salo (201) found an inc eased excretion (over 6 mg/ 24 hrs) in only a fourth of the patients while the average VMA excretion was n th normal range However most authors agree upon the essential role of the symp thetic nervous ystem in the pathoph siology of heart failure In the series of Tomomatsu & Ueba (306) the urinary excretions of A and NA increased with the increasing severity of heart fail e reaching a maximum t grade III but decreased when the heart failure became still more severe (grade IV) An ncrease in the excretion of NA but not of A occurred also in the series of Chidsey *et al* (48) In a fourth of the ad lt patients with heart failure studied by Pekkarinen *et al.* (204) the excretion of A was elevated it was lowest, however in the most severe cases of heart failure Th finding in the present children's series of a low VMA excretion n the two most severe cases of heart failure is in harmony with the above observations.

I the l ght of these findings, the activation of the sympathetic nervous system and the urinary excretion of A and NA as well as of their metabol tes seem to depend at least in part on the grade of severity of the heart failure A smaller activation of A, NA and VMA excretions than might be expected in severe cases of heart failure in ad lts and children may be due to fluid retention which

SUMMARY

The purpose of the present study was mainly to determine the normal values of urinary VMA excretion and their limits in Finnish children during childhood. A kind of screening study was also performed on the standard child patient series in a children's hospital, and special attention was paid to certain disease groups that were of interest from the aspect of VMA excretion

The series under study comprised 619 children under 15 years of age 389 of whom constituted a normal conditions series and 230 a pathological conditions series

The VMA determinations from 24 hour urine collections were made according to the micromodification by Pekkarinen & Hakulinen (199) of the method of Pisano *et al* (221) The values have been corrected for recovery loss In comparisons of the results the VMA excretion values calculated per kilogram of body weight were mainly used

The most important findings were as follows

Normal conditions

1 The mean urinary VMA excretion of fullterm newborn infants on the first day of life was low (55 μg/kg pe 24 hrs) It was twofold this value on the 4th day of life and threefold at the age of about 2 weeks being then on the average excretion level of the entire childhood when calculated per kilo gram of body weight. — Cesarean section and the duration of the second stage of delivery had no significant effect on the VMA excre tion

2 The mean urinary VMA excretion per kilogram of body weight of prematures on the first days of life and at the age f abcut 2 weeks was the same respectively as that of the fullterm newborn controls and of the 2 week-old controls regarded as normal in th n VMA excretion.

3 Olde infant and ch ldren

a) Urinary VMA xcretion in μg/kg per 24 hr The mean VMA excretion values were presented for the different age groups childhood (Table 5) For healthy child between 2 and 15 years the calculated m VMA excretion was 105 (S E.M = ± 2 S = ± 22) μg/kg per 24 hrs and the ra values of the mean ± 2 S D were 61— μg/kg per 24 hrs. *These values (rounded to 60—150) are regarded as the nor range of VMA excretion for Finnish chil over 2 years of age*

The results for selected hospitalized child showed that the above values can be app in practice also to the age period of 6— months, while in younger infants VMA cretions up to 200 μg/kg per 24 hrs occur even in normal conditions.

The differences between the mean VM excretions in the various age groups children were small but low excretion pe were seen in the age groups of 1—6 mont 2—4 years and 8—10 years, which also show significant differences from the excretions the adjacent age groups

The VMA excretion per kilogram of bo weight was considered to be the most relia expression for the activity of urinary VM excretion in childhood up to prepuberty

b) Urinary VMA excretion in mg per 24 h The mean VMA excretion values in mil grams per 24 hours were presented for t different age groups of childhood (Table 5).

The correlations calculated on the basis the mean values in the various age grou showed that the 24 hour urinary VMA excr tion of children aged 2—15 years correlat well with age (r=0 99 p<0 001) and also, a function of age with body weight (r=0.9 p<0 001) and the 24 hour urine volume (r 0 97 p<0 001) A correlation was observ also between very high, and conversely ve low urine volumes and their respective VM excretions.

The annual increment in the mean VM exc etion was greatest in the first year life (0 94 mg/24 hrs per year) and smalle

at preschool age (0 17 mg/24 hrs per year) A slight rise in the annual increment (to 0 35 mg/24 hrs per year) occurred at about the age of 10 years, after which it decreased abruptly In the light of earlier studies it was assumed that this annual increment in the VMA excretion, which ran parallel to the annual increment in body weight till prepu berty was mainly a reflection of the quantita tive development of the noradrenergic nervous system.

4 The mean content of VMA in the 24 hour urine varied in the different age periods of childhood. On the 1st and 2nd days of life it was high (4 9—4 7 µg/ml per 24 hrs) later in the first three months low (1.5—2 1 µg/ml per 24 hrs) and in children older than these it was at the level of the 1st and 2nd days of life (3.6—5 1 µg/ml per 24 hrs).

5 No sex difference was seen in the values of 24-hour VMA excretion of healthy children aged 2—15 years when all the age groups were combined. On the other hand, when th individual age groups were analyzed the VMA excretion of boys aged 2—4 years was found to be slightly higher than that of girls of the same age ($p < 0.05$)

6 The diurnal rhythm observed in ch ldren by earlier investigators was conf rmed in th study in children over 2 years of age

7 The mean urine ol mes per 24 hours and their dispersions in the different age groups of childhood were presented (Table 5)

Pathological conditions

1 Increased urinary VMA excretion alues were observed in children in the following groups

a) Certain child patients who had undergone a surgical operation had clearly levated post operative VMA excretions (up to 388 µg/kg per 24 hrs) On the other hand, the mean VMA excretion on the 1st and 2nd post operative days of 20 children over 2 years of age who had undergone various operations were not significantl elevated o er those of the controls.

b) In congenital heart disease with heart failure a few h ldren had distinctl elevated VMA excretions (up to 531 µg/kg per 24 hrs) but in 10 urin samples from 7 infants with heart failure the mean VMA excretion was not significantl higher than the mean in the control series of selected hospitalized children. In compensated heart failur and in congenital heart disease without symptoms of heart failure the VMA excret ons generall were normal.

c) The mean VMA excretion per kilogram of body weight (154 ± 16 µg/kg per 24 hrs) of febrile patients with infectious diseases (temperature ≥ 39 0°C w signif cantl higher ($p < 0.01$) than in the control series There also wa a significant pos tiv orrelation ($r = 0.55$, $p < 0.01$) between the individual VMA excretion and the body temperature

d) Children with acute bronchial sthma had a s gnificantly elevated mean VMA excretion (15 ± 16 µg/kg per 24 hrs, $p < 0.01$ on the first day in hospital. On the 2nd and 3 d days of treatment the mean VMA excretion showed a tendency to decrease coincidentally with a distinct improvement in the clinical state

e) Children who were given an exchange transfusion of blood on the first day of life because of hemolytic disease of the newborn had on the 2nd day of l fe a somewhat h gher mean VMA excretion ($p < 0.05$) than the controls.

f) The VMA excretions of a child w th neuroblastoma and one with pheochromocytoma were highly elevated (up to 32.5 and 35 4 mg per 24 hrs) In both cases the VMA excretion correlated well with the course of the disease

As a first tumor suspect limit value of VMA excretion for the chemical diagnosis of pheo chromocytoma, paraganglioma or a tumor of the neuroblastoma group is recommended 150 µg/kg per 24 hrs Provided other severe diseases can be excluded alues exceeding 200 µg/kg per 24 hrs in children gi strong reason to suspect the above tumors and require careful additional examination (N B These alues should be applied to tumor diagnosis n adults with certain reservations only since in iew of the higher body weight they are likely to be too high.)

2 Decreased urinary VMA excretion values were seen in the following cases

a) One patient with cho ea minor had an extremely low mean VMA excretion (4 µg/kg per 24 hrs) The possible reason for this low value was discussed.

b) Decreased VMA excretions were seen in cases of congenital pyloric stenosis (down to 38 µg/kg per 24 hrs). The possibility of a metabolic factor in addition to im renal function was discussed.

c) In addition to the above cases, decreased VMA excretions were observed in a girl with paraplegia due to a tumor in the lumbar spinal cord, in two children with renal disease with anuria in addition to uremia, in three children with hepatic disease who had elevated serum GOT and bilirubin concentrations, and in one child with severe heart failure.

ACKNOWLEDGEMENTS

The determinations of vanilmandelic acid in the present investigation were carried out at the Department of Pharmacology of the University of Turku, the head of which Professor Aimo Pekkarinen, M.D. had suggested to me the subject of study. As an experienced scientist in the field of adrenaline and noradrenaline and their metabolism he had special qualifications to competently direct this work. Under his guidance was also developed the micromodification of the method of vanilmandelic acid used in this investigation. For all this I owe him my deep gratitude.

The majority of the pediatric patients studied were hospitalized in the Children's Hospital of the University of Turku. I wish to express my sincere thanks to Professor Tuomas Peltonen, M.D. head of the Hospital for the support and advice that he generously gave me in many ways. I warmly thank also Associate Professor Kauko Kouvalainen, M.D. of the same Hospital, who without sparing time or trouble read my manuscript and offered me much valuable advice.

For the opportunity to compile the series of newborn infants I am deeply indebted to Professor Lauri Rauramo, M.D. head of the Obstetrical and Gynecological Hospital of the University of Turku. My best thanks are also due to the midwives and children's nurses of his hospital who with great care performed the urine collections and solicitously treated the babies' "bottoms" that often were irritated by the procedure.

With the kind permission of Professor Ole Wasz-Höckert, M.D. I received from the Children's Hospital of the University of Oulu, head of which he is, a large considerable part of the samples of urine from premature newborn infants. I am very grateful to him for this.

To my good friends, Associate Professor Esko Iisalo, M.D. Docent Olli Castrén, M.D. Acting Rector of the University of Kuopio and Docent Matti Dahl, M.D. I tender cordial thanks for stimulating discussions and constructive advice in the course of the years this investigation was in progress.

I am most grateful to Mrs. Seija Linnaluoto and Mrs. Tuulikki Pekkalainen who carried out the determinations of vanilmandelic acid with great skill and care. Mr. Tauno Pasanen, M.Sc., performed the statistical calculations and Mrs. Raili Kuvaja drew the graphic figures, and I warmly thank them for pleasant co-operation.

I owe special thanks to gratitude for Mrs. Aili Ryynänen librarian of the medical library of the University of Turku and to her colleagues, all of whom possess the admirable quality of rendering willing and painstaking service unto their neighbor.

This report was translated by Miss Elvi Kaukokallio and Miss Arra Aalto Hum.Cand., to both of whom I extend thanks for well performed work.

I wish to thank Miss Marja Hakulinen for her technical help and Mrs. Lea Heiskanen, Mrs Aira Nevalainen, Mrs. Orvokki Vuori and Miss Aino Räsänen for their secreterial assistance.

The parents of numerous children as well as many child welfare institutions and schools in Turku, Varkaus and Kuopio helped me greatly by collecting urine samples from both healthy and sick children. I hold their generous assistance in great esteem.

Finally I wish to tender sincere thanks to my wife Inkeri who has bravely borne all the inconveniences that a wife will be called upon to endure when work of this kind is in process. Not to speak of my young sons, who all too often have had to hear the definite "No not now" from their father's lips.

Kuopio January 1971

Alpo Hakulinen

REFERENCES

1. Aleksandrow D., Januszewicz, W & Woclal, B. Urinary excretion of epinephrine norepinephrine and vanilll mandelic acid in patients with myocardial infarction *Pol Med J 6* 1 1967
2. Allegranza, A. Bozzi, R. & Bruno, A. Urinary excretion of 5-hydroxy ndoleacetic homovanillic and vanillmandelic acid i schizophrenics taking reserpine and hlorpromazine *J Nerv Ment Dis, 140* 207 1965
3. Ambanelli, U & Starcich, R.: Comportamento delle catecholamine plasmatiche rinarie nelle sindromi coronariche Aspetti clinici farmacodinamici dell' escrezione dell acido anilmandel o. *G Clin Med 44* 682, 1963
4. Anthony P P Coles, H M T Pryse Davies, J & Sinclai L. Biochemical, pharmacological, and histochemical studies in neuroblastoma. *Arch Dis Child 40* 411 1965
5. Anton A. H & Greer M The effect of serpine on catecholamine metabolism and behaviour in retarded children. *Clin Pharmacol Ther 7* 727 1966
6. Armstrong, M D & McMillan, A. Identification of major urinary metabolite of norepinephrine *Fed Proc 16* 146 1957
7. Armstrong, M D McMillan, A. & Shaw K. N F 3 methoxy-4-hydroxy D-mandelic acid urinary metabolite of norepinephrine *Biochim Biophys Acta, 25* 422, 1957
8. Arnett, E. L. & Watts, D T Cat cholamine excretion in men exposed to cold *J Appl Physiol, 15* 499 1960
9. Axelrod, J The formation, metabolism, uptake and release of noradrenaline and adrenaline *In* H Varley & A H, Gowenlock (eds.) *The clinical chemistry of monoamines.* West European symposia on clinical chemistry Elsevier Amsterdam 1963, vol 2, p 5.
10. Axelrod, J Metabolism and inactivation of noradrenaline and the effect of drugs. *I* G. B. Koelle W W Douglas & A. Carlsson (eds.) *Proceedings of the 2nd international pharmacological meeting* Pharmacology of cholinergic and adrenergic transmission Pergamon Press, Oxford 1965, vol 3, p 205.
11. Axelrod, J The metabolism of catecholamines I n and in vitro *Pharmacol Rev 11* 402, 1959
12. Axelrod, J Metabolism of epinephrine and other sympathomimetic amines *Physiol Rev 39* 751 1959
13. Axelrod, J o-methylation of epinephrine and other catechols in vitro and in vivo *Science 126* 400, 1957
14. Axelrod, J & Tomchick, R Enzymatic o-methylation of epinephrine nd other catechols. *J Biol Chem, 233* 702, 1958
15. Axelrod, J Weil Malherbe H & Tomchick, R The physiological disposition of H -epinephrine and its metabol metanephrine *J Pharmacol Exp Ther 127* 251 1959
16. Bäckström Järvinen, L H ights and eights of Finnish hildren nd young adults. *Ann Paediat Fenn 10* Suppl. 23 1964
17. Be uvallet, M Fugazz J & Sol M Nouvelles récherches sur les variations saisonnières de la nor adrénaline cérébrale *J Physiol* (Paris), *54* 289, 196
18. Bell, M Observations on the biochemical diagnosis of neuroblastoma. *I* C. Bohuon (ed.) *Neuroblastomas, biochemical studies Recent results in cancer research.* Springer Berl 1966 ol 2, p 42.
19. Bell M & Steward, J K. Neuroblastoma and cat holamine excretion. *Lancet, I* 1061 1961
20. Berman, M L. & Pettit, J A U inary excr ion of 3-methoxy-4-hydroxymandelic acid afte ex al stress situations. *J Lab Clin Med 57* 126, 1961
21. *Birkmayer W Der alpha Methyl P Tyrosin-Effekt* bei extr pyramidalen Erk ankungen. *Wien Klin Wschr 81* 10 1969
22. Blair R. G Phaeochromocytoma and pr gnancy Report of case nd review of 51 cases *J Obstet Gynaec Brit Cwlth, 70* 110, 1963
23. Boehm, J J & O Brien, D. The urinary ex cretion of 3-methoxy-4 hyd oxy-mandelic acid (VMA) in newborn infants with the respiratory distress syndrome *Pediatrics, 31* 841 1963
24. Bohuon, C. Données récentes sur la biochimie des neuroblastomes. *Rev Franç Etud Clin Biol, 9* 165 1964
25. Bozzi, R. Bruno, A. & Allegranza, A. Urinary metabolites of some monoamines nd clinical effects under reserpine and chlorpromazine. *Brit J Psychiat, 111* 178 1965.
26. Brunjes, S. Catecholamine metabolism I essential hypertension *New Eng J Med, 271* 120, 1964
27. Brunjes, S., Castner E & Hodgman, J Catecholamine metabolism in newborn infants *Clin Res, 12* 88 1964
28. Brunjes, S., Castner E. Wybenga, D. & Arterberry J D Hypertension and abnormal catecholamine deactivation *Clin Res, 12* 76 1964
29. Brunjes, S. & Haywood, L. J A ontrolled study of the antihypertensive response to an MAO inhibitor B Urinary excretion of cate holamines and their metabol tes *Ann NY Acad Sci, 107* 982 1963
30. Brunjes, S Lew M & Arterberry J D Catecholamine metabolism in thyroid disease *Clin Res, 12* 114 1964

Byers, S O Friedman, M Rosenman, R H & Freed, S C Excretion of 3 methoxy 4 hydroxy mandelic acid in men with behavior pattern associated with high incidence of coronary artery disease *Fed Proc, 11* 99, 1962

Calandre L, Bonel, S & Vega, P E luation de l'acide anilmandelique (VMA) dans l'urine des personnes saines et des patients avec hypertension artérielle *Abstr IV Europ congr cardiol,* Prague Czech Med Pres 1964 p 31

Campus, S Fabris, F Rappelli, A, Mathis, I Effetti de la trinitroglicerina sull'escrezione urinaria di catecholamine ed acido anilmandelico. I Nei soggetti normali *Boll Soc Ital Biol Sper 43* 304 1967

Campus, S Rappelli, A Fabris, F & Mathis, I Escrezione urinaria di catecholamine ed acido vanil mandelic nel cane dopo blocco dei recettori beta adrenergici Nota preliminare *Boll Soc Ital Biol Sper 43* 306, 1967

Cannon, P J Whitlock, R T Morris, C Angers, M & Laragh, J H Effect of alpha-methyl DOPA in severe and malignant hypertension *JAMA, 179* 673, 1962.

Caprioara, D Dean M & Vlaicu, L The changes of the urinary catecholamines adrenaline noradrenaline and vanil-mandelic acid in hypertension of pregnancy. *Acta Endocr* (Copenhagen Suppl *119* 156, 1969

Castren, O Urinary excretion of noradrenaline and adrenaline in late normal and toxemic pregnancy Effect of rest, work, and reserpine treatment *Acta Pharmacol* (Copenhagen) *20* Suppl 2 1963.

Castren, O Kaartinen, N & Saarikoski, S The metabolism of H –noradrenaline in human placental and foetal tissue homogenates *Ann Chir Gynaec Fenn, 57* 405, 1968.

Castrén, O Pekkarinen, A & Sorva, K Urinary excretion of free adrenaline and noradrenaline by newborn infants *Ann Chir Gynaec Fenn,* 2 114 1963

Cawte, J E Phenylketonuria *Med J Aust 2* 13, 1954

Cession, G van Cauwenberge H & Lecomte J Elimination urinaire de l'acide 4 hydroxy 3 methoxymandelique chez la femme enceinte normale *C R Soc Biol* (Paris), *1 7* 1826 1963

2 Cession, G Lecomte J & Cauwenberge, H Etude chez la femme de la teneur en amines sympathiques du liquide amniotique et du tissu placentaire *C R Soc Biol* (Paris), *158* 920, 1964

1 Cession-Fossion, A Lebotte G & Chantraine J M Elimination urinaire des catécholamines et de leur metabolite l'acide vanillylmandelique chez l'enfant normal *Acta Paediat Belg, 18* 104 1964

Chatten, J & Voorhees, M L Familial neuroblastoma *New Engl J Med, 277* 1230, 1967

3 Cheek D B Bondy R K & Johnson, L R The effect of mercurous chloride (calomel) and epinephrine (sympathetic stimulation) on rats The importance of the findings to mechanisms in infantile acrodynia (Pink disease *Pediatrics, 23* 302 1959

6 Cheek, D B Malinek, M & Fraillon, J M Plasma adrenaline and noradrenaline in the neonatal period, and infants with respiratory distress syndrome and placental insufficiency *Pediatrics, 31* 374 1963

47 Cheek, D B & Rowe R D Aspects of sympathetic activity in the newborn, including the respiratory distress syndrome *Pediat Clin N Amer 13* 863, 1966

48 Childers C A Baumwald, F & Morrison A G Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure *Amer J Med, 39* 412, 1965

49 Christacos, K B Constantinos, N S Agathopoulos, A S Matsaniotis, N & Danelatou-Athanassiadis, C Metabolism of aromatic amino acids in collagen diseases Urinary excretion of 3 methoxy 4 hydroxymandelic acid and the interference of 3 methoxy 4-hydroxy phenylpyruvic *Clin Chim Acta, 1* 1 5, 1967

50 Clark, A C L Moore A E & Null, M Metabolites of catecholamines in the urine of children with tumours of neural crest origin *Aust Paediat J 1* 4., 1965

51 Closen, R & Michaelis, J Untersuchungen zur Ausscheidung der Katecholamine und ihrer Abbauprodukte bei Hypertonikern und beim Phäochromocytom *Klin Wschr 44* 1161 1966

52 Connelian, T P & Godfrey J M The routine determination of urinary 4 hydroxy 3-methoxy mandelic acid *Clin Chim Acta 9* 410 1964

53 Crout, J R Catecholamine metabolism in pheochromocytoma and essential hypertension. *In* W M Manger (ed.) *Hormones and hypertension* Thomas, Springfield, Ill 1966 p. 3

54 Crout, J R Pheochromocytoma *Pharmacol Rev 18* 651 1966

55 Crout, J R., Pisano, J J & Sjoerdsma, A Urinary excretion of catecholamines and their metabolites in pheochromocytoma *Amer Heart J 61* 375, 1961

56 Crout, J R & Sjoerdsma, A Turnover and metabolism of catecholamines patients with pheochromocytoma *J Clin Invest, 43* 94 1964

57 Curran, D A Hinterberger H Lance J W & Jaffe A D Total plasma serotonin, 5 hydroxy indoleacetic acid and p-hydroxy m-methoxymandelic acid excretion in normal and migrainous subjects *Brain, 88* 997 1965

58 Curzon, G Theaker P & Phillips, B Excretion of 5 hydroxyindolyl acetic acid (5HIAA in migraine *J Neurol Neurosurg Psychiat, 29* 85 1966

59 Dauchy F & J E Gaudicell Nouvelles methodes de dosage de l'acide anilmandelique de la metadrenaline et de la normetadrenaline dans l'urine *Ann Biol Clin* Paris *23* 769, 1965

60 DeLarue N C & O Brien, D Pheochromocytoma important type of curable hypertension A report of 11 cases and review of the literature *Canad J Surg, 6* 259 1963

61 Dengler H Klemm, H & Reichel, G Die Katecholaminausscheidung bei Infektionskrankheiten *Klin Wschr 7* 795, 1959

62 Dienstbier E Balik, J Duchon, J & Fischer O Vylučování kyseliny 3-hydroxyindoloctové kyseliny vanilmandlové nemocných glaukomem *Cesk Oftal 23* 177 1967

REFERENCES

1 Aleksandrow D., Januszewicz, W & Wocial, B. Urinary excretion of epinephrine norepinephrine and anilhylmandelic acid in patients with myocardial infarction. Pol Med J 6 1 1967
2 Allegranza, A., Bozzi, R. & Bruno, A. Urinary excretion of 5-hydroxyindoleacetic homovanillic and vanilmandelic acids in schizophrenics taking reserpine and chlorpromazine J Nerv Ment Dis, 140 207 1965.
3 Ambanelli, U & Starcich, R. Comportamento delle catecholamine plasmatiche e urinarie nelle sindromi coronariche Aspetti clinici e farmacodinamici dell' escrezione dell'acido anilmandelico. G Clin Med, 44 682, 1963
4 Anthony P P Coles, H M T Pryse-Davies, J & Sinclair L. Biochemical, pharmacological, and histochemical studies in neuroblastoma. Arch Dis Child 40 411 1965.
5 Anton A. H & G M The effect of reserpine on catecholamine metabolism and behaviour in retarded children Clin Pharmacol Ther 7 727 1966
6 Armstrong, M D & McMillan, A. Identification of major urinary metabolite of norepinephrine Fed Proc 16 146 1957
7 Armstrong, M D McMillan, A. & Shaw K. N F 3-methoxy-4 hydroxy-D mandelic acid urinary metabolite of norepinephrine Biochim Biophys Acta, 25 422, 1957
8 Arnett, E L & Watts, D T Catecholamine excretion in men exposed to cold. J Appl Physiol 15 499 1960
9 Axelrod, J The formation, metabolism, uptake and release of noradrenaline and adrenaline In H Varley & A H Gowenlock (eds.) The clinical chemistry of monoamines West European symposia on clinical chemistry Elsevier Amsterdam 1963 vol. 2, p. 5.
10 Axelrod, J Metabolism and inactivation of noradrenaline and the effect of drugs. In G B Koelle W W Douglas & A Carlsson (eds.) Proceedings of the 2nd international pharmacological meeting Pharmacology of cholinergic and adrenergic transmission Pergamon Press, Oxford 1965 vol. 3, p 205
11 Axelrod, J The metabolism of catecholamines in vivo and in vitro. Pharmacol Rev 11 402 1959
12 Axelrod, J Metabolism of epinephrine and other sympathomimetic amines. Physiol Rev 39 751 1959
13 Axelrod, J o-methylation of epinephrine and other catechols in vitro and in vivo Science 126 400, 1957
14 Axelrod, J & Tomchick, R Enzymatic o-methylation of epinephrine and other catechols J Biol Chem, 233 702, 1958
15 Axelrod, J Weil-Malherbe H & Tomchick, R The physiological disposition of H -epinephrine and its metabolite metanephrine J Pharmacol Exp Ther 127 51 1959
16. Bäckström-Järvinen, L. Heights and eights of Finnish children and young adults. Ann Paediat Fenn 10 Suppl 23, 1964
17 Benmiloud, M Fugazza, J & Sol M Nouvelles recherches sur les variations saisonnières de la noradrénaline cérébrale J Physiol (Paris), 54 285, 196_
18 Bell M Observations on the biochemical diagnosis of neuroblastoma. In C. Bohuon (ed.) Neuroblastomas, biochemical studies. Recent results in cancer research Springer Berlin 1966, vol 2, p. 42.
19 Bell, M & Steward, J K. Neuroblastoma and catecholamine excretion. Lancet 1 1061 1961
20 Berman, M L & Pettit, J A Urinary excretion of 3-methoxy-4-hydroxymandelic acid after several stress situations. J Lab Clin Med 57 126, 1961
21 Birkmayer W Der alpha Meth l-P Tyrosin-Effekt bei extrapyramidalen Erkrankungen Wien Klin Wschr 81 10, 1969
22 Blair R. G Phaeochromocytoma and pregnancy Report of case and review of 51 cases J Obstet Gynaec Brit Comm, 70 110, 1963.
23 Boehm, J J & O Brien, D The urinary excretion of 3-methoxy-4 hydroxy mandelic acid (VMA) in newborn infants with the respiratory distress syndrome Pediatrics, 31 861 1963.
24 Bohuon, C. Données récentes sur la biochimie des neuroblastomes Rev Franç Etud Clin Biol, 9 165, 1964
25 Bozzi, R Bruno, A. & Allegranza, A. Urinary metabolites of some monoamines and clinical effects under reserpine and chlorpromazine Brit J Psychiat, 111 176, 1965.
26 Brunjes, S. Catecholamine metabolism in essential hypertension. New Eng J Med 271 120, 1964
27 Brunjes, S Gartner E & Hodgman, J Catecholamine metabolism in newborn infants. Clin Res, 12 88 1964.
28 Brunjes, S., Gartner E., Wybenga, D & Arterberry J D Hypertension and abnormal catecholamine derivation Clin Res, 12 78, 1964
29 Brunjes, S. & Haywood, L J A controlled study of the antihypertensive response to an MAO inhibitor B. Urinary excretion of catecholamines and their metabolites. Ann NY Acad Sci, 107 982, 1963.
30 Brunjes, S Levy M & Arterberry J D Catecholamine metabolism in thyroid disease Clin Res, 12 114 1964

metrals after intravenous injection of dl-norad renaline -C[14] J Clin Invest 4 1373, 1963
98 Goodall, McC., Rosen, L. & Kirshner N. Catabolism of dl-adrenaline -C[14] and effect thereon of marsilid. Fed Proc, 17 56, 1958
99 Green, M Cooke R. E. & Lattanzi, W. Occurrence of chronic diarrhea in three patients with ganglioneuromas. Pediatrics, 23 951 1959
100 Greenberg R. E. & Gardner L. I. Catecholamine metabolism in functional neural tumor J Clin Invest 39 1729 1960
101 Greenberg, R. E. & Gardner L. L. The excretion of free catecholamines by newborn infants. J Clin Endocr 20 1207 1960
102 Greenberg, R. E. & Gardner L. I. New diagnostic test for neural tumors of infancy increased urinary excretion of 3-methoxy-4-hydroxy mandelic acid and norepinephrine in ganglioneuroma with chronic diarrhea. Pediatrics, 24 683, 1959
103 Greenberg, R. E. & Lind, J. Catecholamines in tissues of the human fetus. Pediatrics, 27 904 1961
104 Greenberg, R. E., Lind, J. & Euler U. S. Effect of posture and insulin hypoglycemia on catecholamine excretion in the newborn. Acta Paediat Scand, 49 780 1960
105 Greer M. & Williams, C. M. Biochemical studies in neuroblastoma. Clin Res, 11 46, 1963
106 Greer M. & Williams, C. M. The sympathetic neurohormones in pheochromocytoma, neuroblastoma and dysautonomia. Trans Amer Neurol As, 88 223, 1963.
107 Griffin, M. E. & Bolande R. P. Familial neuroblastoma with regression and maturation to ganglioneurofibroma. Pediatrics, 43 377 1969
108 Haluhinen, A. O. the excretion of vanilmandelic acid (VMA) in different age groups of children and in certain clinical conditions Acta Physiol Scand, Suppl 27 66, 1966
109 Haluhinen, A. Urinary vanilmandelic acid (VMA) excretion of normal children Scand J Clin Lab Invest, Suppl 110 190 1969
110 Haluhinen, A., Harvonen, L. & Pelkonen, T. Response of blood pressure to sucking and tilting in the newborn infant Ann Paediat Fenn, 8 56, 1962.
111 Halme A. Pekkarinen, A. & Turunen, M. O. the excretion of noradrenaline adrenaline 17-hydroxycorticosteroid and 17 ketosteroids during the postoperative stage Acta Endocr Copenhagen, 24 Suppl 3., 19 7
112 Harrison, T. S. & Seaton, J. The relative effects of hypoxia and hypercarbia on adrenal medullary secretion anaesthetized dogs J Surg Res, 5 560 1965
113 Henrotte J. G. Labrune G. & Dresse A. L'excretion urinaire de l'acide 3-methoxy mandelique dans différentes populations humaines Arch Int Pharmacodyn 1 2 782 1963
114 Hermann N. & Mornex, R. Human tumours secreting catecholamines Pergamon Press Oxford 1964
115 Hertting G. & Axelrod, J. Fate of tritiated noradrenaline at the sympathetic nerve endings Nature London 189 17 1961
116 Hintze & Kreppel, F. Über den Einfluss der Lageänderung auf Herzfrequenz Blutdruck und Katecholaminausscheidung im Harn bei Säuglingen, Kleinkindern und älteren Kindern. Kl. Wschr 1071 1964
117 Hunzenberger G. & Buhler, R. Die Ausscheidung von 3-Methoxy-4-Hydroxy-Mandelsäure (Vanillinmandelsäure VMS) im Harn von intern erkrankten Patienten Helv Ak 16 1961
118 Howard, W. F. M Devitt, P. J. & Stander R. W. Catecholamine content of the mural cord blood urine of the newborn. Amer J Obstet Gynec 8 615, 1964
119 Hume D. M. The neuroendocrine response to trauma in the adult and in the child Amer J Surg 99 43 1960
120 Iisalo E. & Laurila, S. A clinical trial with new antihypertensive drug ST 155 Catapresan Curr Ther Res, 9 353 1967
121 Iisalo E. & Pekkarinen, A. Vanilmandelic acid excretion in cancer patients Int C Res 1 1968
122 Imhof P. Hedlager F. & Kaeser H. Über Kreislaufregulationsstörungen und Veränderungen der 3-Methoxy-4-Hydroxy-mandelsäure-Ausscheidung im Urin nach traumatischer Querschnittläsion des Rückenmarks. Helv Med Acta 29 1 3, 1962
123 Inamori, Y Kawa, A. Ogawa, T. Takeda, S. Okamoto O. & Kanehisa, T. Urinary excretion rate of 3-methoxy-4-hydroxy-d-mandelic acid (VMA) in rats emotional behaviours in the rat Acta Med Univ Kagoshima, 163, 1967
124 Isaacs, H. Medlabe M. & Polliner W. M. Noradrenaline-secreting neuroblastomas. Brit Med J 1 401, 1959
125 Ishida, N. Metabolism of catecholamines in hyper and hypothyroid patients. Tohoku J Exp Med, 78 78, 196
126 Iwase M. Urinary excretion of free catecholamine and 3 methoxy-4 hydroxy-mandelic acid in patients with peripheral vascular diseases and their level following adrenomedullectomy J Nagoya Med As, 86 103, 1963, Cited in Excerpta Med (Amst.), Sect. IX, 18 No 7839 1964
127 Jackson, R. L. Hanna, F. M. & Flynn, M. A. Nutritional requirements of infants and children. Pediat Clin N Amer 9 879 1962
128 Jacobs, S. L. Sobel, C. & Henry R. J. Excretion of 3-methoxy-4-hydroxy-mandelic acid and catecholamines in patients with pheochromocytoma J Clin Endocr 21 315 1961
129 Jones, W. P. G. Circulatory collapse associated with defective catecholamine metabolism Human Med J 29 101 1963.
130 Kaeser H. Catecholamine-producing neural tumors other than pheochromocytoma Pharmacol Rev 18 659 1966
131 Kaeser H. Bettex, M. & Stadman, W. Further observations on the determination of catecholamine metabolites in tumours of sympathetic nervous system Arch Dis Child, 39 165 1964
132 Kaeser H. Eberhardt, M. Seller, K. & Cornu, F. Über das Verhalten der 3-Methoxy-4-H drox mandelsäure im Urin unter diagnostischen Insulinbelastungen Helv Paediat Acta 18 17 1963
133 Kaeser H. Schweingarth, O. Seller, K. & Spengler G. A. Die klinischen Bedeutung der Bestimmung von Katecholaminmetaboliten bei Tumoren Helv Med Acta, 30 421 1963

134 Kaeser H. & Studnitz, W Urine of children with sympathetic tumors. The excretion of 3-methoxy-4-hydroxy-mandelic acid. *Amer J Dis Child, 102* 199 1961

135. Kaeser H & Wagner P Mechanism of action of alpha methyldopa. *In* C. Bohuon (ed.). *Neuroblastomas, biochemical studies. Recent results in cancer research*, Springer Berlin 1966, vol. 2, p. 33.

136 Kalliomäki, J L., Saarimaa, H A & Seppälä, P O Effect of alpha-methyl-dopa on blood pressure, peripheral skin temperature and urinary excretion of 3-methoxy-4 hydroxy-mandelic acid in arterial hypertension and in rheumatoid arthritis. *Curr Ther Res*, 5 291 1963.

137 Kandrac, M Langeh, J Talacova, M & Cronekova, M Blood pressure and the metabolites of catecholamines eliminated in various clinical disorders. *Abstr 4th Europ congr cardiol*, Prague Czech Med Press 1964 p 157

138. Kärki, N T The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variation and the effect of muscular work on it *Acta Physiol Scand 39* Suppl. 132 1956.

139 Kärki, N T Kuntzman, R & Brodie B. B Norepinephrine and serotonin brain levels at various stages of ontogenetic development *Fed Proc 19* 23., 1960.

140. Karlberg P Moore R. E. & Oliver T K., J The thermogenic response of the newborn infant to noradrenaline *Acta Paediat Scand, 51* 284 1962.

141 Karlson, P Sekeris, C. E. & Herrlich, P Über neue Dopaminmetaboliten im Harn beim bösartigen Phäochromozytom. *Deutsch Med Wschr 88* 1373, 1963

142. Kasil, G. N Grabchenkov N I Matlina, E. S & Borva, E. M Simpato-adrenalovaia sistema pri ostrol cherepno-mozgovoi travme *Dokl Akad Nauk SSSR, 158* 1455—1458, 1964

143 Kelleher J Walters, G., Robertson, R & Smith, P Chemical test for phaeochromocytoma. *J Clin Path, 17* 399 164

144 Kenmoch J S., Symington, T & Woodger B A. Chemical and histochemical observations in benign and malignant phaeochromocytoma *J Path Bact 81* 409 1961

145 Kenny F M Malvaux, P & Migeon, C J Cortisol production rate in newborn babies, older infants, and children. *Pediatrics, 31* 360 1963

146 Kirshner N The metabolism of (alpha-¹⁴C) (±)-adrenaline in the cat *In Adrenergic mechanisms* Ciba Foundation symposium jointly with committee for symposia on drug action Churchill, London 1960 p 45

147 Kirshner N Goodall McC & Rosen, L Metabolism of dl-adrenaline 2-C¹⁴ in the human *Proc Soc Exp Biol Med 98* 627 1958

148 Klein, D & Chernaik, J M Determination of urinary 3-methoxy-4 hydroxy-mandelic acid (vanillylmandelic acid) by paper electrophoresis *Clin Chem, 7* 257 1961

149 Knauff, H G Fruhmann, G & Verbeck, G Die Ausscheidung von Adrenalin und Noradrenalin bei Asthma bronchiale und bei Lungenemphysem *Klin Wschr 40* 411 1962

150 Koch, P Lefebvre P Lemieux, R. & Laurin, C. Histamine induced aryl-mandelic aciduria in the schizophrenic and the non-schizophrenic psychiatric patient. *Amer J Psychiat 119* 464, 1962.

151 Kogut, M D. & Kaplan, S. A Systemic manifestations of neurogenic tumors. *J Pediat, 60* 694 1962.

152. Koh, W H. & Lee S. J Urinary excretion of vanillylmandelic acid in normal Korean adults and in patients with primary hypertension. *Yonsei Med J 6* 33, 1965.

153. Kolesov D V Vydelenie svobodnykh katekholaminov mochoi period pristupov bronkhialnoi astmy *Pediatriia, 44* 56, 1965.

154 Kontras, S. B. Urinary excretion of 3-methoxy 4 hydroxymandelic acid in children with neuroblastoma. *Cancer 15* 978, 1962

155. Kontras, S. B. Urinary excretion of 3-methoxy 4 hydroxy-mandelic acid in children with neuroblastoma. *Cancer Chemother Rep 16*. 443 1962

156. Kopin, I J Technique for the study of alternate metabolic pathways, epinephrine metabolism in man. *Science 131* 137., 1960

157 Kopin, I J Biochemical aspects of release of norepinephrine and other amines from sympathetic nerve endings. *Pharmacol Rev 18* 513. 1966.

158. Kopin, I. J Storage and metabolism of catecholamines the role of monoamine oxidase *Pharmacol Rev 16* 179 1964

159 Kopin, I J & Gordon, E. K. Metabolism of administered and drug released norepinephrine 7 H in the rat. *J Pharmacol Exp Ther 140* 207 1963.

160. Kopin, I. J & Gordon, E. K Metabolism of norepinephrine H³ released by tyramine and reserpine *J Pharmacol Exp Ther 138* 351 1962.

161 Koren, Z Eckstein, B., Brzezinski, A. & Sulman, F G Adrenaline noradrenaline and serotonin estimations in urine and amniotic fluid during delivery *J Obstet Gynaec Brit Comm, 68* 438. 1961

162 Kraupp, O Bernheimer H Heistracher P Paumgartner G & Schiefthaler Th. 1-(4 Hydroxyphenyl)-2-methylaminoaethanol (Synephrin) im Harn eines Falles mit Hochdruckkrisen. *Wien Klin Wschr 73* 712 1961

163 Kraupp, O Stormann, H Bernheimer H & Obermaus, H Vorkommen und diagnostische Bedeutung von Phenolsäuren im Harn beim Phäochromocytom *Klin Wschr 37* 76, 1959

164 Kumento, A. & Kulonen, E Urinary excretion of 3-methoxy 4 hydroxymandelic acid in Finnish twins *Acta Genet (Basel), 15* 319 1965

165 Kunchke, H J Eckmann F Idris, H & Beck, P Untersuchungen über den Wirkungsmechanismus des Phenylpropyl-diphenylpropyl-amins (Segontin) beim Menschen *Verh Deutsch Ges Inn Med, 70* 191 1964

166 LaBrosse E H Axelrod, J Kopin, I J & Kety S S Metabolism of 7 H -epinephrine-d bitartrate in normal young men *J Clin Invest 40* 253 1961

167 LaBrosse E. H Mann, J D & Kety, S. S. The physiological and psychological effects of

intravenously administered epinephrine and its metabolism, in normal and schizophrenic men III Metabolism of 7 H³-epinephrine as determined in studies on blood and urine *J Psychiat Res, 1* 63, 1961

168 Lamcara, P Gilardi, F F & Marconi, U. Eli minazione urinaria dell'acido 3-metossi, 4-idrossi mandelico nell'ipertensione essenziale *Atti Accad Med Lombard, 17* 369, 1962.

169 Lees, M. H Catecholamine metabolite excretion of infants with heart failure *J Pediat 69* 259 1966.

170 LeMola, S Pagliaro, L. & Marmano, V Urinary excretion of methoxy-vanillic acid and catecholamines in patients treated with bretylium tosylate *Lancet, II* 993 1962.

171 Levine, R. J., Oates, J A Vendsalu, A. & Sjoerdsma, A. Studies on the metabolism of aromatic amines in relation to altered thyroid function in man *J Clin Endocr 22* 1242, 1962

172 McDonald, R. K. & Weise V K. The effect of certain psychotropic drugs on the urinary excretion of 3-methoxy-4-hydroxymandelic acid in man. *J Pharmacol Exp Ther 136* 26 1962

173 McDonald, R. K. & Weise V K. The excretion of 3-methoxy-4-hydroxymandelic acid in normal and in chronic schizophrenic male subjects. *J Psychiat Res, 1* 173, 1962

174 McKendrick, T & Edwards, R. W. H The excretion of 4 hydroxy 3-methoxy-mandelic acid by children. *Arch Dis Child 40* 418, 1965.

175 McMillan, M. Identification of hydroxytyramine in chromaffin tumour *Lancet II* 284 1956

176 Mahler D J & Humoller F L. A comparison of methods for determining catechol amines and 3-methoxy-4 hydroxymandelic acid in urine *Clin Chem, 8* 47 1962.

177 Mann, J D & LaBrosse E H Urinary excretion of phenolic acids by normal and schizophrenic male patients *Arch Gen Psychiat* (Chicago) *1* 547 1959

178 Marmano V & Pagliaro, L Osservazioni su un metodo di dosaggio semiquantitativo dell'acido 3 metossil-4-idrossimandelico *Progr Med* Napol *18* 106, 1962

179 Marshall, P B The relation between anihyl-mandelic acid and 5-hydroxyindoleacetic acid excretion in patient with carcinoid tumor *J Pharm Pharmacol 18* 764 1966

180 Mason, G A Hart Mercer J Millar E J Strang, L B & Wynne N A Adrenaline secreting neuroblastoma in infant *Lancet II* 322, 1957

181 Matsaniotis, N Berats N & Economou Mavrou, C Urinary vanillyl mandelic acid (VMA) excretion by leukemically anaemic children *Arch Dis Child, 43* 372, 1968

182 The metabolism of the catecholamines Clinical implications Combined clinical staff conference of The National Institutes of Health *Ann Intern Med, 6* 960, 1962

183 Migeon, C J Cortisol production and metabolism in the neonate *J Pediat, 55* 280 1959

184 Mills, G C Determination of vanilmandelic acid in urine by anion exchange analysis *Texas Rep Biol Med 23* 753 1965

185 Miyaki H Yoshida, H & Imaizumi, R Determination method for urinary 3-methoxy-4 hydroxymandelic acid and 3 4-dihydroxymandelic acid *Jap J Pharmacol, 12* 79 1962.

186. Morgan, C. D Ruthven, C R. J Sandler M Pantgel, M & Gerard H. Placental transmission and metabolism of catecholamines *Abstr 4th international congress on pharmacology* Basel 1969 p 241

187 Morris, M E & Millar R A Blood pH/plasma catecholamine relationships respiratory acidosis *Brit J Anaesth, 34* 672, 1962

188 Nadler H L. & Hsia, D Y Y Epinephrine metabolism in phenylketonuria *Proc Soc Exp Biol Med, 107* 721 1961

189 Nash, C. W Costa, E. & Brodie B B The actions of reserpine guanethidine and metaraminol on cardiac catecholamine stores *Life Sci 3* 441 1964

190 Nicolopoulos, D Agathopoulos, A Galatsakou-Tharouniadi, M & Stergiopoulos, C Urinary excretion of catecholamines by full term and premature infants. *Pediatrics, 44* 262, 1969

191 Nicolopoulos, D Agathopoulos, A Danelatou Athanassiadou, C & Balatsaki, M Urinary excretion of phenolic and indolic compounds, meta catecholamines, and VMA by fullterm and premature infants. *Pediatrics, 41* 777 1968.

192 Otsuka, A. 1 Studies on the relation of carbohydrate metabolism to urinary catecholamines 2 Studies on urinary catecholamines and urinary excretion of vanillyl mandelic acid under various conditions of carbohydrate metabolism. *Folia Endocr Jap 37* 877 1961

193 Peart, W S Catecholamines and hypertension *Pharmacol Rev 18* 667 1966

194 Pekkarinen, A Adrenaline and noradrenaline in blood and urine *Pharmacol Rev, 6* 35, 1954

195 Pekkarinen, A. Chairman summing up. *In* G B. Koelle W W Douglas & A. Carlsson (eds.) *Proceedings of the 2nd international pharmacological meeting Pharmacology of cholinergic and adrenergic transmission* Pergamon Press, Oxford 1965, vol 3, p. 329

196 Pekkarinen, A Studies on the chemical determination, occurrence and metabolism of adrenaline in the animal organism *Acta Physiol Scand 16* Suppl 54, 1948

197 Pekkarinen, A & Castren, O Excretion of vanilmandelic acid (VMA) in the third trimester of normal and toxaemic pregnancy and other clinical conditions *Ann Chir Gynaec Fenn, 57* 373, 1968

198 Pekkarinen, A Castren, O Iisalo E Koivusalo, M Laihinen, A Simola, P E & Thomasson, B The emotional effect of matriculation examinations on the excretion of adrenaline, noradrenaline and 17 hydroxycorticosteroids into the urine and the content of 17-hydroxycorticosteroids in the plasma *In* J Jilmefelt (ed.) *Biochemistry pharmacology and physiology* symposium Pergamon Press, London 1961 p 117

199 Pekkarinen, A & Hakulinen, A. Micromodification of the determination of vanilmandelic acid (VMA) in urine *Appendix to this publication*

5-Hydroxytryptophan bei Gesunden und Leberkranken. *Klin Wschr 40* 1229 1962.

270. Schmidt, E. & Henning, N. Über den Nachweis der 3-Methoxy-4-Hydroxy-Mandelsäure im Harn. *Klin Wschr 41* 566 1963

271. Schmidt, E., Rosenbusch, U. Henkel K., Schwemmle K. & Schön, H. 5-Hydroxytryptamin und Erkrankungen der Verdauungsorgane. *Gastroenterologia* (Basel) *96* 273 1961

272. Schmid, E. Zicha, L. & John, W. Über die Ausscheidung der Vanillinmandelsäure und anderer Phenolsäuren im Harn bei Lebergesunden und Leberkranken und ihre Beeinflussung durch Glukagon. *Z Gastroent 2* 214 1964

273. Schweisguth, O. Intérêt pour le pédiatre des dosages d'acide vanillylmandélique dans les urines. *In* C. Bohuon (ed.) *Neuroblastomes, biochemical studies. Recent results in cancer research.* Springer Berlin 1966, vol. 2, p. 42.

*274 Shankel, S., Baumjes, S. & Johns, V. J. Jr. A new in vivo assay of monoamine oxidase activity. *Clin Res, 10* 90, 1962.

275. Sheps, S. G., Kottke B. A., Tyce G. M. & Flock, E. V. Effect of methyldopa on the metabolism of catecholamines and tryptophan in metastatic pheochromocytoma. Report of two cases. *Amer J Cardiol, 14* 641 1964

276. Sicuteri, F. Franchi, G. Michelacci, S. & Salmon, S. Aumento della escrezione dell'acido vanilmandelico — catabolita delle catecolamine — durante l'accesso emicranico. *Settim Med 50* 15 1962

277 Sjoerdsma, A. Catecholamine-drug interactions in man. *Pharmacol Rev 18* 673 1966

*278 Sikma, J. & Brouckova, V. Urinary excretion of catecholamines and 3-methoxy-4-hydroxymandelic acid after psilocybin in psychosis. *Acta Nerv Sup* (Praha), *6* 219 1964

279 Smellie J. M. & Sandler M. Secreting intrathoracic ganglioneuroma. *Proc Roy Soc Med, 54* 327 1961

280 Smith, A. A. & Dancis, J. Exaggerated response to infused norepinephrine in familial dysautonomia. *New Eng J Med, 270* 704, 1964

281 Smith, A. A., Taylor T. & Wortis S. B. Abnormal catechol amine metabolism in familial dysautonomia. *New Eng J Med, 268* 705 1963.

282 Smith, R. A., Whitehead, T. P. Morris, L. & Williams, H. P. Functionally active intrathoracic neuroblastoma. *Arch Dis Child 36* 82 1961

283 Sonka, J. Petrášek, J. Žbirková, A. & Slabochová, Z. Vliv redukčních režimů na vylučování 3-metoxy-4-hydroxymandlové (vanilmandlové) kyseliny (Influence of reducing regimens on the excretion of 3-methoxy-4-hydroxymandelic (vanilmandelic) acid). *Česk Gastroent Výž, 17* 430, 1963

284 Sova, J. Karlíček, V. Topinka, I. & Lange N. Vliv hexamethonia na exkreci vanilmandlové kyseliny ... diastolické hypertenze. *Čas Lék Česk 106* 250 1967

*285 Stackpole R. H. Melicow M. M. & Uson, A. C. Pheochromocytoma in children. Report of 9 cases and review of the first 100 published cases with follow up studies. *J Pediat, 63* 315 1963

286 Stearns, G., Newman, K. J. MacKinley J. B. & J. m, P. C. The protein requirement of children from one to ten years of age. *Ann NY Acad Sci, 69* 857 1958

287 Stickler G. B. & Flock, E. V. Neuroblastoma and ganglioneuroblastoma associated increased urinary excretion of catecholamines. *Cancer Chemother Rep 16* 439 1962.

288. Stickler G. B. Hallenbeck, G. A. & Flock, E. V. Ganglioneuroblastoma associated with chronic diarrhea and increased excretion of catecholamines preliminary report. *Mayo Clin Proc 34* 345, 1959.

289 Stickler G. B. Hallenbeck, G. A., Flock, E. V. & Rosevear J. W. Catecholamines and diarrhea in ganglioneuroblastoma. *Amer J Dis Child 104* 598 196..

290. Studnitz, W. Chemistry and pharmacology of catecholamine secreting tumors. *Pharmacol Rev 18* 645, 1966

291 Studnitz W. Effect of Marsilid on excretion of 3-methoxy-4 hydroxymandelic acid in man. *Scand J Clin Lab Invest 11* 224 1959

292 Studnitz, W. Methodische und klinische Untersuchungen über die Ausscheidung der 3-Methoxy-4-Hydroxymandelsäure im Urin. *Scand J Clin Lab Invest 12* Suppl 48 1960

293. Studnitz, W. Neuroblastoma and catecholamine excretion. *Lancet II* 215 1961.

294 Studnitz, W. On the excretion of 3-methoxy-4-hydroxymandelic acid in patients with serotonin producing tumors. *Scand J Clin Lab Invest, 11* 309 1959

295. Studnitz, W. Über die Ausscheidung der 3-Methoxy-4-hydroxyphenylessigsäure (Homovanillinsäure) beim Neuroblastom und anderen neuralen Tumoren. *Klin Wschr 40* 163, 1962.

296 Studnitz, W. & Hanson, A. Determination of 3-methoxy-4-hydroxymandelic acid in urine by high voltage paper electrophoresis. *Scand J Clin Lab Invest 11* 101 1959

297 Studnitz, W. Kaeser H. & Sjoerdsma, A. Spectrum of catechol amine biochemistry in patients with neuroblastoma. *New Eng J Med, 269* 232, 1963

298 Sturm, A., J. Erhöhtes Vorkommen, Bedeutung und Bestimmung der Vanillinsäure im Harn beim Phäochromoblastom. *Deutsch Med Wschr 88* 1000, 1963

299 Sturm, A. J. Das Verhalten der Katecholamine bei Operationen mit Hilfe des extrakorporalen Kreislaufs. *Klin Wschr 41* 988 1963

300 Sunderman, F. W. J. Measurements of vanilmandelic acid for the diagnosis of pheochromocytoma and neuroblastoma. *Amer J Clin Path, 42* 481 1964

301 Sunderman, F. W. J. Cleveland, P. D. Law N. C. & Sunderman, F. W. A method for the determination of 3-methoxy-4-hydroxymandelic acid ("vanilmandelic acid") for the diagnosis of pheochromocytoma. *Amer J Clin Path, 34* 293 1960.

302 Takkunen, R. L. Anthropometric studies on Finnish children *Ann Paediat Fenn, 8* Suppl 19 1962.

303 Traut, N. A. Schmid, E. & Berne D. Ergebnisse und Probleme klinisch-experimenteller Untersuchungen zum Stoffwechsel biogener Amine. *Arzneimittelforschung, 14* 505 1964.

304 Tesley E. The excretion of vanilmandelic acid

in the urine of children. *Danish Med Bull, 14* 17 1967

305 Thiel, G B. & Garcia, V C. The effect of intravenous histamine on the urinary excretion of epinephrine, norepinephrine and 3-methoxy-4 hydroxymandelic acid in essential hypertension. *Amer J Med Sci, 249* 654 1965

306 Tomomatsu, T & Ueba, Y Cardiac failure and catecholamine *Jap Circ J 30* 49 1966.

307 Tresidder G. C. Tumors of the adrenal medulla. *Brit J Urol, 35* 367 1963

308 Varga, F The respective effects of starvation and changed body composition on energy metabolism in malnourished infants *Pediatrics, 23* 1085 1959

309 Vlachakis, W A Kaltermann, U Cuddy R. P Fried, A H, Smithan, H & Esch, R H Vanillylmandelic acid excretion in labile hypertension subjects its variation and response to norepinephrine and angiotensin infusion. *Amer J Med Sci, 249* 79 1965.

310 Voorhess M L Functioning neural tumors. *Pediat Clin N Amer 13* 3, 1966.

311 Voorhess, M L Urinary catecholamine excretion by healthy children I Daily excretion of dopamine norepinephrine, epinephrine and 3-methoxy 4 hydroxymandelic acid. *Pediatrics, 39* 252, 1967

312 Voorhess, M L & Gardner L I Catecholamine metabolism in neuroblastomas. *Lancet, II* 651 1960.

313 Voorhess, M. L & Gardner L I Studies of catecholamine excretion by children with neural tumors. *J Clin Endocr 22* 126, 1962

314 Voorhess, M L & Gardner L I Urinary excretion of norepinephrine epinephrine and 3-methoxy-4 hydroxymandelic acid by children with neuroblastoma *J Clin Endocr 21* 321 1961

315 Voorhess, M L, Pickett, L K & Gardner L I Functioning tumors of neural crest origin in childhood *Amer J Surg, 106* 35, 1963

316 Vuori, I & Pekkarinen, A Effect of long distance skiing and short maximal physical exertion on the vanilmandelic acid, noradrenaline adrenaline and 17 OHCS response in the urine and plasma *Scand Clin Lab Invest, Suppl 108* 42, 1969

317 Waalkes, T P Sjoerdsma, A Creveling, C R Weissbach, H & Udenfriend, S Serotonin, norepinephrine and related compounds in bananas *Science 127* 648, 1958

318 Walker W F Adrenal response to cardiac surgery *Proc Roy Soc Med, 58* 1015, 1965

319 Warkany J & Hubbard D M Acrodynia and mercury *J Pediat, 42* 365, 1953.

320 Weil-Malherbe H Studies on the estimation of 3-methoxy-4 hydroxymandelic acid (VMA) in human urine *Anal Biochem, 7* 485, 1964

321 Weise V K MacDonald, R K & LaBrosse E H Determination of urinary 3 methoxy 4 hydroxymandelic acid in man *Clin Chim Acta, 6* 79, 1961

322 Whalby L G The diagnosis of phaeochromocytoma by laboratory tests *Scot Med J 0* 289 1965

323 Whitby L G Axelrod, J & Weil-Malherbe H The fate of H3-norepinephrine in animals *J Pharmacol Exp Ther 132* 193, 1961

324 Wilk, S Gitlow S E Mendlowitz, M Franklin, M J Carr H E & Clarke, D D A quantitative assay for vanillylmandelic acid (VMA) by gas-liquid chromatography *Anal Biochem, 13* 544 1965

325 Williams, C M & Greer M Gas chromatography of urinary aromatic acid in pheochromocytoma *Clin Chim Acta, 11* 495, 1965

326 Williams, C M & Greer M Homovanillic acid and vanilmandelic acid in diagnosis of neuroblastoma *JAMA, 183* 836 1963

327 Wiswell, J G Hurwitz G F Coronho, V Bing, O H L & Child, D L Urinary catechol amines and their metabolites in hyperthyroidism and hypothyroidism *J Clin Endocr 23* 1102, 1963

328 Wocial, B The comparison of three different method of determination of vanillin-amygdalic acid in urine of healthy people (chromatografic colorimetric and electrophoretic method *Pol Arch Med Wewnet 33* 173, 1963

329 Worwood, A J & Knight, R The determination of 3-methoxy-4-hydroxymandelic acid in urine *J Clin Path, 14* 302, 1961

330 Wood J W & Apers, H Effect of reserpine and guanethidine on excretion of 3-methoxy 4 hydroxymandelic acid in man. *Proc Soc Exp Biol N.Y. 114* 107 1963

331 Wurtman, R J Catecholamines concluded *New Eng J Med 273* 746, 1965

332 Zeisel, H Abbauprodukte der Catecholamine im Harn des Kindes *Z Kinderheilk, 86* 19 1961

333 Zeisel, H & Koschik H J Die Catecholamine Adrenalin und Noradrenalin im Harn des Kindes. *Klin Wschr 37* 1163

334 Zicha, L & Ali, B. S. Über den Einfluss von Koffein auf den Tagesrhythmus der Vanillinmandelsäure Vanillinsäure und Homovanillinsäure *Med Welt 21* 1674 1969

335 Zicha, L & Engelhardt, J Über den Einfluss von Sulfonylharnstoff, ACTH und Metopiron auf Endprodukte des Katecholaminstoffwechsels beim Diabetes Mellitus *Acta Endocr* (Copenhagen), *54* 153, 1967

336 Zicha, V L Schmid, E Süss, E Weiss, P & Bergner D Über das Verhalten der Nebennierenrinden-Steroidausscheidung im Harn und ihre Beziehung zur Vanillinmandelsäure bei emotioneller Belastung durch zahnärztliche Behandlungsmaßnahmen *Endokrinologie 47* 281 1965

337 Zicha, L Schmid, E Weiss, F & Winkler E. Der Einfluss von Glucagon, Insulin, Adrenalin und Sulfonylharnstoffen auf Blutzucker und Vanillinmandelsäure im Harn bei gesunden Kontrollpersonen, Leberkranken und anderen Patienten mit Dysproteinämie *Verh Deutsch Ges Inn Med, 71* 499 1965

338 Ziegler W Die Bedeutung der Vanillin Mandelsäure (VMS für die Diagnostik des Phäochromocytoms und für die Untersuchung des Katecholamin Stoffwechsels *Helv Med Acta, 27* 647 1960

339 Yamamoto, T Catecholamine and inflammation *Kobe J Med Sci, 10* 141 1964

340 Young, R B Stecker D D Bongiovanni, A M., Koop, C E & Eberlein, W R Urinary vanil mandelic acid (VMA) excretion in children Use of simple semiquantitative test *J Pediat, 62* 844 1963

5-Hydroxytryptophan bei Gesunden und Leberkranken. *Klin Wschr 40* 1229 1962

270. Schmid, E. & Henning, N Über den Nachweis der 3-Methoxy-4 Hydroxy Mandelsäure im Harn. *Klin Wschr 41* 566, 1963

271 Schmid, E., Rosenbusch, U., Heinkel, K., Schwemmle, K. & Schön, H 5-Hydroxytryptamin und Erkrankungen der Verdauungsorgane *Gastroenterologia* (Basel) 96 275 1961

272. Schmid, E., Zicha, L. & John, W., Über die Ausscheidung der Vanillinmandelsäure und anderer Phenolsäuren im Harn bei Lebergesunden und Leberkranken und ihre Beeinflussung durch Glukagon. *Z Gastroent*, *2* 214 1964

273. Schweisguth, O Intérêt pour le pédiatre des dosages d'acide vanillylmandélique dans les urines. *I* C. Bohoon (ed) *Neuroblastomas, biochemical studies Recent results in cancer research* Springer Berlin 1966 vol. 2, p 42

274 Shankel, S., Brunjes, S. & Johns, V J Jr A new in vivo assay of monoamine oxidase activity *Clin Res, 10* 90, 1962.

275 Sheps, S G Kottke, B A., Tyce, G M & Flock, E. V Effect of methyldopa on the metabolism of catecholamines and tryptophan I metastatic pheochromocytoma. Report of two cases. *Amer J Cardiol, 14* 641 1964

276. Securri, F Franchi, G., Michelacci, S. & Salmon, S. Aumento della escrezione dell'acido I mandelico — catabolita delle catecolamine — durante l accesso emicranico *Settim Med, 50* 13 1962.

277 Sjoerdsma, A. Catecholamine-drug interactions in man. *Pharmacol Rev 18* 673, 1966

278 Slíma, J & Broucková, V Urinary excretion of catecholamines and 3-methoxy 4 hydroxymandelic acid after psilocybin in psychosis. *Activ Nerv Sup* (Praha), *6* 219 1964

279 Smellie J M. & Sandler M. Secreting intrathoracic ganglioneuroma *Proc Roy Soc Med, 54* 327 1961

280 Smith, A. A. & Dancis, J Exaggerated response to infused norepinephrine in familial dysautonomia *New Eng J Med, 270* 704 1964

281 Smith, A A Taylor T & Wortis, S B. Abnormal catechol amine metabolism in familial dysautonomia *New Eng J Med, 268* 705 1963

282 Smith, R A., Whitehead, T P Morris, L & Williams, H P F nctionally activ intrathoracic neuroblastoma *Arch Dis Child 36* 82, 1961

283. Sonka, J Petrášek, J Žbirková, A & Slabochová, Z. Vliv redukčních režimu na vylučování 3-metoxy-4-hydroxymandlové (vanilmandlové) kyseliny (Influence of reducing regimens on the excretion of 3 methoxy-4-hydroxymandelic (anil mandelic) acid). *Cesk Gastroent Výz, 17* 430, 1963

284 Sova, J Karlíček, V Topinka, I & Lange N Vliv histaminu na exkreci vanilmandlov kyseliny diastolické hypertenze. *Cas Lek Česk, 106* 250 1967

285 Stackpole R H Melicow M M & Uson, A C Pheochromocytoma in children Report of 9 cases and review of the first 100 published cases with follow-up studies *J Pediat 63* 315 1963

286 Stearns, G Newman, K J MacKinley J B & Jeans, P C. The protein requirements of children from one ten ears of age *Ann NY Acad Sci, 69* 857 1958

287 Stickler G B. & Flock, E. V Neuroblastoma and ganglioneuroblastoma associated increased urinary excretion of ca echolamines. *Cancer Chemother Rep 16* 439 1962

288 Stickler G B Hallenbeck, G A. & Flock, E V Ganglioneuroblastoma associated with chronic diarrhe and increased excretion of catecholamines. preliminary eport. *Mayo Clin Proc 34* 548, 1959

289 Stickler G B., Hallenbeck, G A Flock, E. V & Roseveare J W Catecholamines and diarrhea in ganglioneuroblastoma. *Amer J Dis Child 104* 598 1962.

290 Studnitz, W Chemistry and pharmacology of catecholamine secreting tumors. *Pharmacol Rev 18* 645 1966

291 Studnitz, W Effect of Marsilid on excretion of 3-methoxy-4 hydroxymandelic acid I man *Scand J Clin Lab Invest, 11* 224 1959

292 Studnitz, W Methodische od klinische Untersuchungen über die Ausscheidung der 3-Methoxy 4-Hydroxymandelsäure im Urin. *Scand J Clin Lab Invest, 12* Suppl. 48, 1960

293 Studnitz, W Neuroblastoma and catecholamine excretion *Lancet II* 215, 1961

294 Studnitz, W On the excretion of 3-methoxy 4 h droxymandelic acid in patients ith serotonin producing tumors. *Scand J Clin Lab Invest 11* 309 1959

295 Studnitz, W Über die Ausscheidung der 3-Methoxy-4 hydroxyphenylessigsäure (Homovanillinsäure) beim Neuroblastom und anderen neuralen Tumoren. *Klin Wschr 40* 163 1962.

296 Studnitz, W & Hanson, A. Determination of 3-methoxy-4-hydroxymandelic acid in urine by high oltage paper electrophoresis *Scand J Clin Lab Invest, 11* 101 1959

297 Studnitz W Kaeser H & Sjoerdsma, A. Spectrum of catechol amine biochemistry in patients with neuroblastoma *New Eng J Med 269* 232, 1963

298 Sturm, A J Erhöhtes Vorkommen, Bedeutung und Bestimmung der Vanillinsäure im Harn beim Phäochromoblastom *Deutsch Med Wschr 88* 1000 1963

299 Sturm, A., Jr Das Verhalten der Katecholamine bei Operationen mit Hilfe des extrakorporalen Kreislauf *Klin Wschr 41* 988 1963

300. Sunderman, F W J Measurements of anil mandelic acid for the diagnosis of pheochromocytoma and neuroblastoma *Amer J Clin Path, 42* 481 1964

301 Sunderman, F W J Cleveland, P D Law N C & Sunderman, F W A method for the determination of 3 methoxy-4 hydroxymandelic acid ("anilmandelic acid") for the diagnosis of pheochromocytoma *Amer J Clin Path, 34* 293, 1960

302 T kkunen, R L. Anthropometric studies on Finnish children *Ann Paediat Fenn, 8* Suppl 19 1962.

303 Tautz, N A Schmid, E & Berne D. Ergebnisse und Probleme klinisch-experimenteller Untersuchungen zum Stoffwechsel biogener Amine *Arzneimittelforschung, 14* 303, 1964

304 Tenley E The excretion of vanilmandelic acid

APPENDIX

MICROMODIFICATION OF THE DETERMINATION OF VANILMANDELIC ACID (VMA) IN THE URINE

AIMO PEKKARINEN and ALPO HAKULINEN

From the Department of Pharmacology (Head Professor Aimo Pekkarinen M D) Uni ersity of Turku Turku Finland

A number of method ha e been employed for the determination of vanilmandelic acid (VMA, 3-methoxy-4 hydroxymandelic acid) from urine, such as chromatography (1 12) high oltage electrophoresis (15 16) low voltage electrophoresis (4) spectrophotometry (11 13 17) isotope dilution method (19) and gas chromatography (20 21)

Sandler & Ruthven (14) ha e recently described t length the various methods for VMA determination, of wh ch the method of Pisano *et al.* (11) has often been used fo the routine determination of VMA. It is based upon ethyl acetat extraction, re-extrac tion into potassium carbonate oxidation of VMA with sodium periodate in lkal ne solution at 50°C to n llin extracted by toluene and determined spectrophotometrically in potassium ca bonat at 360 mμ

Pisano s method has been technically modified by O Brien and Ibbot (5) and Connelian and Godfrey (2) In the latter method singl set of 100 ml cyl ndrical short stemmed separatory funnel with self locking plastic toppers used instead of Pisano s four series of entrifuge tubes n which th number of p pett ngs can be duced I his mod fication Weil Malherbe (18) used copper ion as oxidizer instead of sodium periodate The results obtained with th method corresponded to those of Pisano s method, but the author prefers Pisano s method owing to ts rapidity Besides its elative quickness, the ad antages of Pisano s method e that it places no requirements as to diet (11 13) and no expensive special laboratory equipment is needed. It requires however ery big centrif ge tubes (50 ml) and rather large quantities of organic sol ents.

W ha e developed a micromod fication from the Pisano method for the determination of VMA. The micromodification, which does not essentially make the method less accurate makes it possible to use smaller amounts of urine and eagents and considerably smaller thick walled test tubes, without glass grinding only with plastic stoppers. In order to re duc the number of p pettings, several reagents have been combined into one solution. For the removal of the discarded layer of solvents, glass capillary uct on is connected to plastic tube and egulated by a string The method i suitable for the determination of larg series. One person can in two day determine a series of at least 20 samples (about 50 test t bes, the blank and standard t bes included) or alternatively a series of 12—15 samples (total 30—36 test tubes) day

Reagents

Ethyl acetate	chromatographic grade	E. Merck AG
Toluene	pro analysi	
Hydrochloric acid	(6 N)	
Acetic acid	(5 N)	
Sodium chloride		
Sodium metaperiodate	(2% in water)	
Sodium metabisulfite Na_2S_20	(10% in water)	B D H
Potassium phosphate dibasic	reagent grade (3 M)	J T Baker
Potassium carbonate	pro analysi (1 M)	E. Merck AG
Cresol red	(0 04% in water)	

D1 3 methoxy-4 hydroxymandelic acid (vanil mandelic acid, VMA) from the California Corporation for Biochem cal Research, Los Angeles, Calif) VMA stock standard (1mg/ml) in 0 01 hydrochloric acid VMA working standard 90 µg/ml) in distilled water

Combined solutions No 1 One part of 6 N hydrochloric acid and 7 parts of distilled water No 2 60 ml of 3 M potassium phosphate dibasic and 30 ml of 5 N acetic acid and 5 ml of 0 04% cresol red

Test-tubes

Half of the test tubes needed were ordinary thick walled (to prevent breakage) test tubes with mm 716 x 160 mm, volume about 21 ml) furnished with polyethylene plastic stoppers, and the other half were conical centrifuge tubes (volume about 8 ml) with polyethylene plastic stoppers. For p petting small amounts of solutions (<1 ml) the Linderström—Lang constriction pipettes are used to obtain greater accuracy

Sampling of urine

A 24 hour urine is collected into a brown bottle containing as preservative either 10 ml of 6 N hydrochloric acid (Pisano) or 20 ml of 10% (v/v) sulfuric acid in adults. In children 0.5 ml of 6 N hydrochloric acid per 100 ml of the expected urine volume is used. The urine is stored frozen or for a short time at +4C.

DETERMINATION

1 Pipet into the 21 ml test tubes with mm 0 8 ml of urine, pH 2—3 (however 1 6 ml of children s urine since their urine is more diluted) 1 6 ml of combined solution No 1 up to saturation point 1 2 g of sodium chloride and 12 ml of ethyl acetate. For the inner standard measure into 5 test tubes 0 8 ml (or 1 6 ml) of urine and the same substances as above, and additionally 0 4 ml of the VMA working standard For the extraction of VMA the tubes are then shaken for 10 minutes in a horizontal shaking machine (shaking amplitude 65 mm, rate 120/min) and centrifuged for 5 minutes.

2 Ten ml of the ethyl acetate layer con taining VMA is transferred into the test tubes (the same size as before) on the bottom of which 1.2 ml 1 M potassium carbonate ha been pipetted for extraction of VMA The tubes are shaken for 6 minutes and centrifuged for 5 minutes. The ethyl acetate layer is removed carefully with a glass capillary tube using vacuum suction.

3 Two of the 8 ml conical centrifuge tubes are taken for each urine extract and one for each urine extract with VMA standard. Into the bottom of one of these two conical centrifuge tubes with urine extract or urine extract with VMA standard (not on the walls) 0 04 ml of 2% sodium meta periodate is accurately pipetted, but not into the other simultaneous centrifuge tube for the blank, into wh ch 0 04 ml of 10% sodium metabisulfite is first pipetted in the sam way From the 21 ml test and standard tubes 0 4 ml of potass um carbonate VMA extract is transferred into the conical test VMA standard and blank tubes The tubes are shaken carefully by hand in order to mix th oxidizing substance after which they are put into a 50 °C water bath for 60 minutes Then the tubes are immediately cooled with water and are usually left standing over night at 4°C. It is also pos ble to continue

the method further on the same day Into the blank tubes is added 0 04 ml of 2% sodium periodate and into the test and standard tubes 0 04 ml of 10% sodium meta bisulfite To neutralize the sample and to control its pH 0 6 ml of comb ned solution \ 2 is added, and 4 ml of toluene is added into all the tubes (the tubes are shaken by hand a few times to remove the carbon dioxide the color of the sample should be yellow). Then the tubes are shaken for 6 min in a horizontal shaking machine and centrifug ed for 5 m n for extraction of VMA into the toluene

4 Into the following tubes 0.5 ml of 1 M potassium carbonate solution is pipetted and 3 ml of toluene extract is then shaken in the horizontal shaking machine and centrifug ed as above The supernatant toluene layer is carefully removed by glass cap'llary suction. The potassium carbonate i transferred into milk glass microcuvette with a 10 mm light pathway (1.5 mm x 10 mm x 25 mm) taking care that no potas ium bicarbonate air bubbles are formed, and then measured with a Beckman DB Spectrophotometer at a wave length of 360 mμ. When controll ng th specificity the measuring can also be carried out at the wavelengths of 330 and 347 mμ, at which both VMA and p-hydroxymandelic acid can be calculated by means of an equa tion (5).

SPECTROPHOTOMETRIC DETERMINA TION AND CALCULATION OF RESULTS

By rais ng th microcuvett to measuri g height (e g by means of small rubber stopper under the cuvette) the milk glas microcuvettes can be used directly in the Beckman DB Spectrophotometer for measuring without microadapter slit. The microcuvettes should be washed carefully several times with distilled w ter befor the measurement of optical density so that the d stilled water maintains ts zero reading of optical density in the two microcuvettes when they are inter changed. The sa nples and blanks re measured aga nst the w ter blank in the microcuvett The samples ar read a Pisano original method t w elength 360 mμ although the bsorption maximum of anilin is t w length 347 mμ, beca use the p-hyd oxymandelic acid (absorptio maximum at 330 mμ) that normally appears in the urine till at 347 mμ causes absorption to some extent For practical purposes, measurement at 360 mμ is quite sufficient.

1 If the reading of the specific optical density of VMA in 0 8 ml urine sample is =V—Bl (the optical density of urine sample — blank) and the specific opt cal density for 8 μg of VMA standard of the urine sample (after reduction of sample reading of urine) =M and the daily urine olume is =Vm (ml) the amount of VMA n mg in the urine is obta ned by the follow ng equation

$$\frac{(V-Bl) \times 8\ (=\mu g\ standa\ d) \times Vm\ (ml)}{M \times 0\ 8\ ml \times 1\ 000} =$$

$$\frac{(V-Bl) \times Vm}{M \times 100} = mg\ VMA$$

2 If the vol me of the original urine sample is 1 6 ml (=in children) the divisor is M x 200 In patients w th a highly elevated VMA excretion and a high optical density reading for VMA, as in pheochromocytoma, paraganglioma or neuroblastoma, th aliquot of potassium carbonat extract of VMA is further diluted with 1M potassium carbonate for n optical measurement

Results

The standard deviation of VMA method standards ± 6 2% in 519 individual daily urine samples in daily routine work (Table 1) (for 0 8 ml ine samples and 8 μg VMA standard the S D is ± 7 2% in 123 samples, and for 1 6 ml urine samples and 8 μg VMA standard it is ± 5 7% in 396 urine samples. The standard deviation of daily means of VMA method standards (Table 2) i ± 4 4% in 96 urine samples (for 0 8 ml urine and 8 μg VMA standard the S D ± 3 9%, and for 1 6 ml urine and 8 μg VMA standard it is ± 3 6%).

The mean recoveries of the 4 8 and 16 μg of the VMA method standards from the 0 8 ml urine samples (Table 3) are 76 8% (17 samples), 78.5% (15 samples) and 82 6% (17 samples) respectively (as compared w th the optical density of equimolar amounts of anilin standard added first to the r reagent of 1 M potassium hydroxide for aliquots), and their standard

Table 1 *The standard deviation of UMA method standards (8 μg) in individual urine samples in daily routine work as the mean of optical density of UMA standard added into the urine I=8 μg/0.8 ml, II=8 μg/1.6 ml urine III=I+II results combined. Mean=Optical density (10 mm light pathway at 360 mμ)*

I		II		III	
Mean	37.6	Mean	38.9	Mean	38.5
n=	123	n=	396	n=	519
S.D	±2.7 (=∓7.2%)	S.D	±2.2 (=∓5.7%)	S.D	±2.4 (=∓6.2%)
S.E.M.	±0.24	S.E.M.	±0.11	S.E.M.	±0.10

Table 2 *The standard deviation of daily means of UMA standards (5 standards daily) in the urine as the mean of optical density of UMA standard I=8 μg/0.8 ml, II=8 μg/1.6 ml urine III=I+II results combined Mean=Optical density (10 mm light pathway at 360 mμ)*

I		II		III	
Mean	37.6	Mean	38.9	Mean	38.5
n=	23	n=	73	n=	96
S.D	±2.2 (=∓5.9%)	S.D	±1.4 (=∓3.6%)	S.D	±1.7 (=∓4.4%)
S.E.M.	±0.45	S.E.M.	±0.17	S.E.M.	±0.17

Table 3 *The mean optical densities (10 ml light pathway at 360 mμ) and the recovery percentage of UMA method standards (4—16μg in 0.8 ml urine) with S.D and S.E.M., as compared with the optical density of equivalent of vanillin standard in 1 M potassium carbonate solution. N=number of samples*

VMA	Optical density Mean	N	S.D	S.E.M.	S.D /	Recovery percent Mean	N	S.D /	S.E.M.
4 μg	20.8	17	±1.38	0.33	6.7	76.8	17	±5.4	±1.3
8 μg	41.1	15	±1.50	0.38	3.6	78.5	15	±2.8	±0.78
16 μg	83.8	17	±1.73	0.42	2.0	82.6	17	±1.6	±0.40

Table 4 *The mean optical densities (10 ml light pathway at 360 mμ) and the recovery percentage of UMA method standards (2—8 μg in 16 ml urine) with S.D and S.E.M., as compared with the optical density of equivalent of vanillin standard in 1 M potassium carbonate solution. N=number of samples*

VMA	Optical density	N	S.D	S.E.M.	S.D /	Recovery percent Mean	N	S.D /	S.E.M.
2 μg	9.6	21	±1.38	±0.33	14.5	73.8	21	∓12.5	∓2.7
4 μg	19.1	21	±1.33	±0.3	7.2	72.3	21	∓4.2	∓0.9
8 μg	38.7	20	±1.35	±0.3	3.5	74.0	20	∓2.8	∓0.6

Table 5 *Precision of the method in the simultaneous determination of UMA of same urine sample in one series as standard deviation of mean UMA content (mg/liter) Four different urine samples*

mg/liter	S.D %	S.E.M.	No. of simultaneous analyses
17.8	3.7	0.15	20
10.3	5.0	0.10	25
6.2	7.6	0.03	36
2.5	8.4	0.03	25

Table 6 *Precision of a single determination of UMA in duplicate urine samples (1.6 ml)*

mg/liter urine	S.D %	S.E.M.	Number of duplicate urine samples
2.03	±4.4	±0.09	23
3.35	±3.4	±0.12	19

Table 7 *Parallel UMA contents (μg/ml) of 86 urine samples of children determined in two methods by reading the final potassium carbonate extraction in the spectrophotometer at the two wavelengths of 330 and 347 mμ (A) and only at 360 mμ (B)*

VMA, μg/ml		(cont.)		(cont.)		(cont.)	
A	B	A	B	A	B	A	B
1.57	1.61	1.05	1.14	4.87	4.53	1.61	1.61
6.68	6.73	1.18	1.24	3.95	3.85	4.65	4.75
6.47	6.50	1.83	1.80	1.22	1.85	2.40	2.41
1.76	1.79	1.93	2.05	2.04	2.08	4.11	4.39
1.75	1.79	2.46	3.06	4.00	4.72	2.37	2.37
1.28	1.19	1.82	1.63	2.05	2.07	1.92	1.85
2.46	2.29	2.89	2.75	2.37	2.40	1.14	1.07
3.14	2.08	4.53	4.55	4.14	4.27	3.52	2.60
0.40	1.06	1.44	1.39	1.24	1.42	8.69	8.85
1.32	1.23	2.37	2.22	0.70	0.78	1.97	1.93
1.89	1.94	1.38	1.27	1.28	1.31	1.77	1.78
2.00	2.01	0.70	0.64	1.39	1.56	1.39	1.44
2.03	2.07	1.45	0.83	4.10	3.94	0.90	0.91
1.27	1.41	4.68	4.57	4.49	2.40	3.82	3.95
1.78	1.79	4.82	3.39	1.73	1.81	2.79	2.89
1.02	1.04	4.00	3.84	2.49	2.52	1.63	1.53
2.22	2.14	2.45	2.45	2.18	2.20	2.08	2.16
1.74	1.58	3.57	3.54	1.71	1.70	1.04	1.15
3.01	2.87	4.57	4.60	1.87	1.88	0.88	0.90
1.75	1.63	4.07	4.59	1.65	1.79	1.63	1.55
2.48	2.44	4.28	4.25	3.78	3.86	—	—
3.12	3.14	5.40	5.44	1.68	1.68	—	—

n	86	86
Mean	2.50	2.46
S.D.	±1.36	±1.33

$p > 0.05$

S(x)% =3.06

Table 8. *The stability of UMA in urine during storage in the refrigeration room up to 4 months and freezing and melting of urine samples 1—3 times*

Number of urine samples	10	10	10
Number of times samples frozen and melted	1	2	3
Length of storage of samples in efrigeration room at —5 C	1 day	2 mos	4 mos
	p>0.05		
Mean VMA content f urine samples (mg/liter)	4.55	4.63	4.21
S.E.M.	±0 70	±0 70	±0.66
	p>0.05		

± 5 4%, ± 2 8% and ± 1 6%, respectively in the different urine samples of the present series.

The mean recoveries of the 2 4 and 8 µg of the VMA method standards from 1 6 ml urine samples (Table 4) are 73 8%, 72.5% and 74 0% (21 21 and 20 samples, re spectively) and the standard deviations of these recovery percents are ± 12 5%, ± 4.2% and ± 2.8%, respectively in the different urine samples of the present series.

Precision of the method (Table 5) used for the simultaneous determinations of VMA of the same urine sample in one series as S D is ± 3 7% and 5 0% when the mean content of VMA is 17.3 mg/l and 10 3 mg/l and ± 7 6% and ± 6 4% when the mean content of VMA in the urine is 6 2 mg/l and 2.5 mg/l.

Precision of a single determination of VMA in duplicate urine samples (Table 6) (1 6 ml) is ± 4 4% (28 duplicates) when the mean content of VMA is 2 03 mg/l and ± 3 4% (19 duplicates) when the mean content of VMA is 3 35 mg/l.

When the final potassium carbonate ex traction was read at a wavelength of 360 mµ, the mean VMA amount in 86 urine samples of children was 2.46 ± 1 33 (S D) µg/ml, and when read at both 330 and 347 mµ and the concentration of each substance (VMA and p-hydroxymandelic acid) was then calculat ed by means of an equation, it was 2 50 ± 1.36 (Table 7) The difference was not significant ($p > 0\ 05$). The standard error of a single determination was 8 06%

The stability of VMA of the urine samples was studied in 10 urine samples (pH 2—3) after storage in the refrigeration room (— C) for periods of 1 day 2 months and 4 month and freezing and melting of the samples three times. No significant change in the mean amount of VMA in these samples was noted during this period at a low temperature (Table 8)

DISCUSSION

The advantage of this micromodification for determination of VMA is the small urine and reagent volumes and serial extraction in simple test tubes without glass stoppers, using only polyethylene stoppers in thick walled test tubes with rims. The method requires micropipets, with which the pipetting is simple and rapid In this method all the reagent volumes are reduced to one fifth of those used by Pisano *et al.* (11) with the ex ception of the amounts of the oxidizing and the reducing agent, which are two-fifths in order to guarantee complete oxidation which is important.

In order to obtain an efficient extraction, special attention must be paid to the in tensity and regularity of adequate and vigorous shaking We use the shaking machine every time with the same known shaking amplitude and the shaking frequency of 120 per minute the first shaking lasting 10 minutes and all the following shakings 6 minutes by means of the rate meter In our modification also the periodate incubation time together with the shaking times are lengthened, because it was observed that these measures increase the completeness and regularity of the re coveries of the VMA standards After the periodate incubation the test tubes were usually in our routine method left standing over night n a refrigerator and the reducing sugstance (sod um metabislufite) was not added

until after this stage Depending on the size of the series it is thus possible to continue the determination after the above mentioned oxidation on the following day or according to the original methods immediately since this circumstance did not have any signif icant effect upon the results.

This method is linear at least at VMA concentrations of 1.25—20 µg/ml in the urine According to Pisano *et al* (11) the optical density of the vanillin sol tion is directly p o portional to concentration in the range of at least 10—100 µg/sample (abt. 2 ml)

By the present method we ha determ ned the urinary VMA n both normal and some clinical situations. During normal military service in which very great strain is avoided 50 conscripts had a mean VMA excretion/24 hrs of 5 2 and 5 26 mg determined on two different days (9). In 18 patients at a mental hospital the mean VMA excretions were correspondingly 4 4 and 4 6 mg (10) and before surgical operations the VMA excretion was 5.8 mg/24 hrs (16 9)

The minimum excretions of patients at the mental hospital were observed after a 5 weeks treatment with 1 2 and 1.5 mg of nialamide (10), while the indiv dual maximum excretions, up to 20 mg/24 hrs, appeared after major operations (6) In cardiac n sufficiency (58 patients) the mean excretions of VMA on the 1st—5th days in hosp tal were only slightly abov the normal (4 9—6 5 mg/24 hrs) and the individual mean ex cretions on 1st—5th day were in only a fourth of these patients over 6 0 mg/24 hrs (ranges over 6 mg 6 0—12 2 mg/24 hrs (7) In renal insufficiency in two groups with in creased serum creatinine content (10 7 a d 2 9 mg/100 ml, the means of 14 and 17 patient) the VMA excretion decreased to 2 4 and 3 2 mg/24 hrs, respectively (8)

In fullterm newborn infants the VMA ex cretion on the 1st—5th days was 55—84 µg/kg per 24 hrs and n prematures on the 2nd—6th days 43—87 µg/kg/24 hrs (5). In selected hosp talized hildren who were ssumed to have a relatively normal VMA excretion it was in the age groups of 7—30 days, 1—6 month and 16—24 month 107 ± 8 (S E.M) 132 ± 11 nd 103 ± 4 µg/kg per 24 hrs, respectively (5) In healthy ch ldren between 2 and 15 years the mean VMA excretion was 105 (S E.M =2 S D = ± 22) µg/kg per 24 hrs. (5)

Before urgical operation for pheochromocytoma the VMA excretion of an adult patient during paroxysmal increases of blood pressure was 34.3—6 3 mg/24 hrs in a 7 year old girl with pheochromocytoma t was pre operatively up to 35 4 mg per 24 hrs and in a 2 year old boy with nueroblastoma 32 5 mg per 4 hrs (5)

SUMMARY

For the urinary determination of anil mandelic acid we dev loped a micromodific tion of Pisano met od 0 8 o 1 6 ml of urine for the sample and t blank combined which is very su table for serial determination Several reagents are combined to ed ce the number of p pettings, and ex ept for two fifths of Pisano s amounts of sodium period ate and sodium metabisulfite the amounts of reagent n urine are generally one f fth of Pisano s. The expensiv glass toppers e substituted by cheap thick walled glass tubes with rim nd pla tic stoppers

From the point of view of ecovery carefull intensive and egular haking and ex traction s ind spensable The rat meter the shaki g mach ne is recommended fo quantitative and regular extract on, as well the same shaking time (10 min for the first extraction and 6 m n fo all the follow ng extraction) The practicab lity of this method has been studied in clinical states in adult and children, as well as after the administra tion of drugs

The recoveries of 4 µg 8 µg and 16 µg of VMA added as method standard to th urine sample are 76 8%, 78.5% and 82 6%, respectively nd the standard deviation of re covery percentages is + 5 4%, ± 2 8% and ± 1 6%, respectively

The standard deviation of optical densities of VMA standard in individual rine samples in daily routine work is ± 6 2% n 519 samples, and the standa d deviation of opti cal densities of daily means of VMA stan dards is ± 4 4%.

Precision of the method used for the sim ltaneou determination of VMA of sam urine sample in one series a S D ± 5 7% and 5 0% when the mea of VMA ar 17.8 mg/l and 10.3

± 7 6% and ± 6 4% when the mean contents of VMA are 6.2 mg/l and 2.5 mg/l respectively in the urine

When the mean VMA content in 86 urine samples of children was calculated from spectrophotometric readings at wavelength of 360 mμ on the one hand, and at 330 and 347 mμ, on the other hand no significant difference was found between the results. The standard error of a single determination was 8 06 %.

No significant change was noted in the VMA content of 10 urine samples (pH 2—3) after storage in the refrigeration room (—5 C) up to 4 months and freezing and melting of the samples three times.

RFFERENCES

1 Armstrong, M D & McMillan, A. Identification of major urinary metabolite of norepinephrine. *Fed Proc 16* 146, 1957

2. Connelan, T P & Godfrey J M The outine determination of urinary 4-hydroxy 3-methoxymandelic acid. *Clin Chim Acta, 9* 410, 1964

3 Hakulinen, A. A. Urinary excretio of vanilmandelic acid of children in normal and certain pathological conditions. *Acta Paed Scand*, Suppl. *212* 1971

4 Klein, D & Chernaik, J M. Determination of urinary 3-methoxy-4 hydroxy mandelic acid (vanillylmandelic acid) by paper electrophoresis. *Clin Chem, 7* 257 1961

5 O'Brien, D & Ibbot, F A.. Laboratory manual of pediatric micro- and ultra macrobiochemical technique Harper & Row New York 1962, p 74.

6. Pekkarinen, A Hakulinen, A & Linna, M Vanillmandelic acid excretion in surgical operations. *T be published*

7 Pekkarinen, A & Iisalo, E Excretion of anil mandelic acid (VMA) in cardiac insufficiency *Ann Med Intern Fenn, 54* 169 1965

8. Pekkarinen A & Iisalo, E. Excretion of vanil mandelic acid (VMA) in patients with renal insufficiency *Ann Med Intern Fenn, 54* 175 1965

9 Pekkarinen, A., Iisalo E Hakulinen, A Linna, M & Rinne, U Excretion of vanilmandelic acid in normal and clinical conditions *Acta Endocr* (Copenhagen) Suppl *100* 140, 1965

10. Pekkarinen, A Rinne, U & Iisalo E Prolonged decrease vanilmandelic (3 methoxy-4 hydroxymandelic) acid excretion by man during and after nialamide treatment *Acta Pharmacol* (Copenhagen) *22* 331 1965

11 Pisano, J J Crout J R & Abraham, D Determination of 3-methoxy 4 hydroxymandelic acid in urine. *Clin Chim Acta* 785 1962

12. Robinson, R Ratcliffe, J & Smith, P A screening test for phaeochromocytoma. *J Clin Path, 12* 541 1959

13. Sandler M & Ruthven, C. R. J The estimation of 4-hydroxy 3-methoxymandelic acid in urine. *Biochem J 80* 78 1961

14 Sandler M & Ruthven, C. R. J The measurement of 4 hydroxy 3-methoxymandelic acid and homovanillic acid. *Pharmacol Rev 18* 343 1966

15. Sato, T Determination of urinary 3 methoxy 4-hydroxymandelic acid by high voltage electrophoresis. *Nisshin Igaku, 47* 827 1960

16. Studnitz, W Methodische und klinische Untersuchungen uber die Ausscheidung der 3 Methoxy 4-Hydroxymandelsäure im Urin *Scand J Clin Lab Invest 12* Suppl 48, 1960

17 Sunderman, F W J Cleveland, P D Law N C & Sunderman, F W A method for the determination of 3-methoxy-4 hydroxymandelic acid ("vanilmandelic acid") for the diagnosis of pheochromocytoma. *Amer J Clin Path, 34* 293, 1960

18 Weil Malherbe H Studies on the estimation of 3-methoxy-4 hydroxymandelic acid (VMA) in human urine *Anal Biochem, 7* 485, 1964

19 Weise, V K MacDonald, R K & LaBrosse E., H Determination of urinary 3-methoxy-4-hydroxymandelic acid in man. *Clin Chim Acta, 6* 79 1961

20 Wilk, S., Gitlow S E Mendlowitz, M., Franklin, M J Carr H E & Clark D D A quantitative assay for vanillylmandelic acid (VMA) by gas-liquid chromatography *Anal Biochem, 13* 544 1965

21 Williams, C M & Leonard, R. H Microanalytical determination of dihydroxyaromatic acids by gas chromatography *Anal Biochem, 5* 362, 1963.

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB Uppsala, Sweden without charge.)

150. Mau, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organisation of the X International Congress of Paediatrics.* Lisbon, 1962. Edited by Bo Vahlquist. Sw kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology Therapy and Prognosis. Sw kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic study. Sw kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Editing by Bo Vahlquist and Arvid Wallgren. Sw kr 25.— 1964
157. Bruns, G., Krüger, K. and Öckerman, P. A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm. 1964. Edited by Y. Larsson. Sw. kr 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Palmrose, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw kr 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966

[illegible] E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., ... A Review of 187 Cases in Children with Follow-... Pulmonary Function Studies in 51. Sw kr. 20.— 1966

... Anna-Lisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr 25.— 1966

...sen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw kr 30.— 1966

168. Trojaborg, W., Focal Spike Discharges in Children. Longitudinal Study. Sw. kr 25.— 1966
169. Dahl, Maria, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Raihma, Margot, Studies on Eosinopenia. Sw kr 30.— 1966
171. Gidlung, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw kr. 20.— 1966
172. *Festschrift in Memory of Constantin Charanzu.* Sw kr 35.— 1967
173. Walsh, S. Zoe, The Electrocardiogram during the First Week of Life. Sw kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr 25.— 1967
175. Illicoskara, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw kr 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen. 1967. Sw. kr 35.— 1967
178. Kjellgren, Irène, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw kr 20.— 1968
181. Koch, Gösta, Lung Function and Acid Base Balance in the Newborn Infant. Sw. kr 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw kr. 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw kr 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw kr. 25.— 1968
185. Andersen, Elm, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw kr 40.— 1968
186. Dunn, Harry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr 25.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I-VI. Sw. kr. 30.— 1969
188. Meeuwisse, Gunnar W. and Melin, Karin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw kr 25.— 1969
189. Pitkänen, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw kr 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr 20.— 1969
191. Kettikko, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr 30.—1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kamonsen, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thern, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr 20.— 1969
197 Bergh, Rolf, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw kr 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr 30.— 1969
200. Bayley, Dora M., Cordeiro, Joaquim, Romeiro, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr 35.— 1970
201. Sutherland, Lynette E., Hartmann, Phyllis, Bahn, John U., Kelley, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw kr 30.— 1970
202. Fomon, Samuel J., Filer Jr, J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw kr 30.— 1970
203 Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw kr 35.— 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effect of Physical Training and Improved Nutrition. Sw kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw kr 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207 Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw kr 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Vaktmeer, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr 35.— 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. Sw kr. 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr 25.— 1971
212. Haluskova, Alena, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971

Price Swed. kr 35 —

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 213 1971

CLINICAL AND MORPHOLOGICAL STUDIES IN CONGENITAL HEART DISEASE

A REVIEW OF 777 CASES

BY BERNHARD LANDTMAN

ALMQVIST & WIKSELL PERIODICAL COMPANY

Tilgmannin Kirjapaino Helsinki
1971

CONTENTS

Introduction 4
Material and methods 5
Results 7
Main cardiac malformations 7
Sex 8
Age at death 8
Birth rank and maternal age 8
Birth weight and condition after birth 8
Physical development and general condition 9
Cyanosis 9
Congestive heart failure 9
Heart murmurs 9
Size of the heart 10
Extracardiac congenital anomalies 10
Other causes of death 12
Postoperative deaths 13
Diagnostic errors 13
Length of hospitalization 13
Operability 13
Discussion 15
Incidence of congenital heart disease in autopsy series 15
Sex, birth rank and birth weight 15
Mortality 16
Extracardiac congenital malformations 16
Other causes of death 16
Diagnostic problems 17
Therapeutic aspects 17
Summary 19
Acknowledgements 21
References 22
Appendix 26

INTRODUCTION

The past two decades have witnessed a growing interest in the study of young infants with congenital heart disease. This interest has been stimulated by the advances made in surgical treatment of cardiac children in this age group. Moreover the major therapeutic problems in pediatric cardiology are confined to early infancy since mortality due to congenital heart disease is comparatively high during the first months of life.

There is still insufficient information on the incidence of congenital malformations of the heart. Reported figures vary considerably as the methods employed differ Autopsy series represent selected cases favouring more serious lesions, while clinical studies alone are unreliable in providing definite diagnosis. Moreover complicated heart lesions with a high early mortality are underrepresented in series consisting predominantly of older patients. Hoffman (63) has recently reviewed the many sources of error involved in comparative studies on the incidence of congenital malformations of the heart.

It is difficult to assess the natural history of different heart anomalies from mortality statistics alone, because such studies tend to ignore the wide spectrum of pathological differences between individual cases. For example, the course of a mild coarctation of the aorta cannot be predicted from mortality rates comprising all varieties of this anomaly Furthermore, a heart defect may often be an incidental autopsy finding in fatal cases in which extracardiac diseases were the primary or main cause of death. In such cases cardiac surgery would hardly have saved the life of the child. Autopsy studies alone are insufficient in assessing the main cause of death because without supplementary clinical information it is difficult, if not impossible, to determine whether or not the heart disease was directly responsible for death. Very few such comparative clinical and post mortem studies in congenital heart disease have so far been published.

The present study is an attempt to summarize the experience gained from patients with congenital heart disease treated and lost at the Children's Hospital in Helsinki during a 23-year period. The problem was approached both from a clinical and a morphological point of view In each case data were collected from the clinical notes made on the patient during hospitalization. These data were supplemented with observations made at post-mortem examinations, which were performed in all cases included in the study Particular attention was paid to the assessment of primary and contributory causes of death and of the possibilities of cardiac operations in conservatively treated cases. It was hoped that a study of this kind might throw some additional light on the many problems involved in the management of seriously ill children with congenital heart disease. Some preliminary results of this study were presented at the annual meeting of the Association of European Paediatric Cardiologists in Warsaw in May 1970 (78)

Finland has a population of 4.6 million. During the period 1947 to 1971 approximately 5 700 patients with congenital heart disease have been studied at the Children's Hospital in Helsinki. The geographical distribution of the patients corresponded by and large to the density of population in the different parts of the country (77). The proportion of new born babies treated at the hospital is comparatively high. Thus, most of the sick neonates born at two maternity hospitals in Helsinki with a total of approximately 13,000 deliveries a year are referred to the Children's Hospital.

A special cardiac clinic has been in existence at the Children's Hospital in Helsinki since 1950. Cardiac operations have been performed at the hospital since 1953 The overall operative and late mortality was 4.7 per cent in the first 1,000 patients operated upon for congenital heart disease (81). To date, over 2,000 of the above mentioned patients with congenital heart disease have undergone cardiac surgery Approximately 1,200 of the conservatively treated patients have died before the age of 16 years. A large number is waiting for admission to the hospital for further studies or operation. The remainder of the children had minor cardiac anomalies for which surgery was not considered indicated. Most patients who have reached the age of 16 years have been referred for follow-up or treatment elsewhere.

Over 90 per cent of the patients who die at the Children's Hospital in Helsinki are studied post mortem. From 1947 to 1970 autopsies were performed on 5,697 patients, of whom approximately 75 per cent were infants under one year of age Congenital malformations of the heart were encountered in 777 (14 per cent) of these autopsies. Only "definite" cardiovascular anomalies were included in the study Thus, a merely patent isolated ductus arteriosus in small infants and minor structural aberrations of the heart and the great vessels were disregarded. Figure 1 shows that the incidence of congenital heart disease in the autopsy series has gradually increased from 4 6 per cent in 1947 to over 20 per cent in recent years.

The 777 patients with congenital heart disease en-

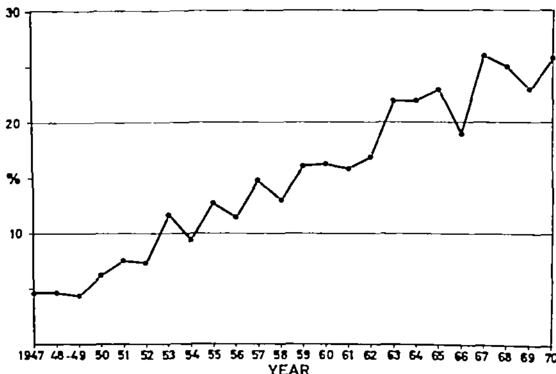


Fig 1 Congenital malformations of the heart were encountered in 777 (14 per cent) of 5 697 autopsies performed on children treated at the Children's Hospital in Helsinki during the period 1947 to 1970. The incidence of cardiac anomalies in consecutive autopsies increased from 4.6 per cent in 1947 to over 20 per cent in recent years.

countered in the autopsy series formed the basis of the present study The case histories, clinical notes and autopsy protocols of the patients were reviewed with regard to the following main data and findings: Main cardiac malformation age of the patient at death, sex, birth rank, birth weight, condition after birth, physical development, symptoms and signs, clinical findings, main laboratory data, extracardiac congenital malformations, pathological changes in other organs, treatment and length of hospitaliza tion (Appendix). Complete information was not available in all cases. Data and findings on which information was lacking were taken into considera-tion in analyzing the results. Cardiac catheterization and/or angiocardiography was performed in 127 cases.

The study also aimed at providing answers to the following questions. Was the heart disease recognized during life? Which was the primary or main cause of death? Was there any association between the occurrence of extracardiac malformations in different groups of cardiac lesions? Could the life of conser vatively treated patients possibly have been saved by cardiac surgery? Needless to say the study was based on observations made by several pediatricians and pathologists working at the Children's Hospital during the period 1947 to 1970. This source of er ror however seems unavoidable in a long-term study of this kind. Approximately one third of the patients were seen by the author

Cardiac operations were performed on 82 of the patients. In addition, 94 patients underwent surgery for other reasons, mostly for extracardiac malforma-tions.

A coding system was used in compiling the clinical and morphological findings and data (Appendix). A total of approximately 30 000 items of information were obtained and analyzed by computer In pre-senting the results, only some main observations will be discussed.

}

Main cardiac malformations. The patients were divided into 12 groups according to the main cardiac defect or syndrome (Table 1). Hemodynamic rather than strictly anatomical aspects were taken into consideration in classifying some of the complicated lesions. There was considerable overlapping between some groups.

Forty-four patients had endocardial fibroelastosis without other cardiac anomalies except for valvular involvement, which was present in 18 of these cases. In addition, fibroelastosis was encountered in 45 patients with other cardiac lesions, particularly hypoplastic left heart syndrome and coarctation of the aorta. Septal defects, patent ductus arteriosus, transposition of the great vessels and truncus arteriosus were associated with endocardial fibroelastosis only in isolated cases. Fibroelastosis was not seen in patients with tetralogy of Fallot and with tricuspid atresia.

A ventricular septal defect was considered the main cardiac malformation in 104 patients, 25 of them had additional cardiovascular anomalies. The size of the ventricular septal defect varied. There were 9 cases of single ventricle. Atrial septal defects were the main lesion in 71 patients 24 of them revealed other cardiovascular anomalies. A single atrium occurred in 11 instances. The group of combined septal defects (51 cases) comprised 26 patients with a common atrioventricular canal and 8 patients with bilocular heart. The defects were complicated by other cardiovascular anomalies in 23 cases.

A large patent ductus arteriosus was present in 47 patients 3 of them had additional cardiac anomalies. Coarctation of the aorta occurred in 74 cases, the preductal type being the commonest variety (54 cases). The coarctation was associated with a patent ductus arteriosus in 63 cases and with intra cardiac anomalies in 27 instances. There were 72 cases of hypoplastic left heart syndrome characterized mainly by a small left ventricle and a hypoplastic aortic arch. Associated lesions such as mitral and/or aortic atresia and a patent ductus arteriosus were common.

Transposition of the great vessels occurred in 102 cases, including 11 cases of double outlet right ventricle. Additional cardiac lesions were very common. Atrial and ventricular septal defects were present in 24 and 59 cases respectively A patent ductus arteriosus occurred in 52 instances and various other cardiovascular lesions were seen in 39 cases.

Table 1 *Diagnostic classification of 777 children with congenital heart disease studied clinically and post mortem at the Children's Hospital in Helsinki during the period 1947—1970*

Main cardiac malformation	No. of cases	Sex		Age at death								
		Boys	Girls	0-7 d	7d-1m	1-3m	3-6 m	6m-1yr	1-3 yrs	3-5 yrs	5-10 yrs	10-16 yrs
Endocardial fibroelastosis	44	26	18	8	5	5	6	6	13	1		
Ventricular septal defect	104	54	50	38	19	10	15	9	4	1	4	4
Atrial septal defect	71	35	36	33	11	11	4	5	4	1	1	1
Combined septal defects	51	24	27	13	9	5	14	2	3	1	1	3
Patent ductus arteriosus	47	18	29	14	10	4	5	6	1	1	2	4
Coarctation of the aorta	74	43	31	23	24	13	3	3	3		3	2
Hypoplastic left heart syndrome	72	45	27	39	23	5	5					
Transposition of the great vessels	102	65	37	20	21	20	20	5	11	2	2	1
Truncus arteriosus	75	44	31	35	12	12	8	5		1	2	
Tetralogy of Fallot	46	27	19	4	5	6	5	8	6	2	7	3
Tricuspid atresia	22	15	7	4	7	2	6	3				
Miscellaneous	69	43	26	21	11	8	8	6	6	3	2	4
Total:	777	439	338	252	157	101	99	58	51	13	24	22

Table 2. *Birth rank of the children in the present study (A) compared with that of 1,610 759 children born alive in Finland in 1950–1968 (B). Figures given as percentages*

	Birth rank							
	1	2	3	4	5	6	7	8–
A.	38	26	18	7	5	2	1	3
B.	36	26	16	9	5	3	2	3

A single vessel emerging from the heart and supplying the pulmonary and systemic circulation was the main feature of heart lesions classified as truncus arteriosus (75 cases) Whether some of the cases should have been classified as tetralogy of Fallot with pulmonary atresia or as hypoplastic left heart syndrome with aortic atresia was a matter of interpretation. Thirty of the patients had other cardiovascular anomalies in addition to a ventricular septal defect, which was present in all cases. There were 46 patients with tetralogy of Fallot 11 of them had complicating cardiovascular anomalies. Tricuspid atresia was considered the main malformation in 22 cases. Associated anomalies were present in all cases.

A miscellaneous group (69 cases) mainly comprised valvular lesions and atresias (33 cases), anomalies of the venous return (13 cases), idiopathic ... il cardiac hypertrophy (10 cases) and isolated cases of Ebstein's malformation of the tricuspid valve, complete atrioventricular block, dextrocardia, anomalies of the coronary arteries, etc. Many of these miscellaneous anomalies were also encountered in the other groups of patients but they were not considered the main cardiac malformation. The incidence of different types of congenital heart disease did not significantly change during the course of the study

Sex The series comprised 439 boys and 338 girls (Table 1). Patients with coarctation of the aorta, hypoplastic left heart syndrome, transposition of the great vessels, truncus arteriosus, tetralogy of Fallot and tricuspid atresia showed a male preponderance, whereas patent ductus arteriosus was more common in girls than in boys. It may be mentioned that of the patients who died before 6 months of age, 59 per cent were boys and 41 per cent girls. There were, on the other hand, slightly fewer boys (48 per cent) that girls (52 per cent) among the patients over 6 months old.

Age at death. Table 1 shows that 252 (32 per cent) of the patients were less than one week and 409 (53 per cent) less than one month of age. Death occurred during the first day of life in 127 (16 per

Table 3 *Percentage of low birth weight (2,500 g or less) and birth asphyxia*

Main cardiac malformation	Low birth weight	Birth asphyxia
Endocardial fibroelastosis	17	25
Ventricular septal defect	41	49
Atrial septal defect	33	35
Combined septal defects	23	50
Patent ductus arteriosus	19	28
Coarctation of the aorta	22	32
Hypoplastic left heart syndrome	25	35
Transposition of the great vessels	10	66
Truncus arteriosus	26	61
Tetralogy of Fallot	18	52
Tricuspid atresia	19	50
Miscellaneous	17	46
Mean	24	46

cent) of the cases. The proportion of neonates did not significantly change during the course of the study Seventy-eight per cent of the patients died before 6 months of age and 86 per cent during the first year of life. Only 9 of the conservatively treated patients were over 10 years old. Table 1 shows that patients with hypoplastic left heart syndrome and with tricuspid atresia had a comparatively high early mortality

Birth rank and maternal age. The order of birth of the patients compared with that of all children born alive in Finland from 1950 to 1968 is shown in Table 2. Thirty-eight per cent of the patients were the first born child. The order of birth did not differ from that of Finnish children in general. The birth rank showed a similar pattern for patients with different types of cardiac malformations. It may be mentioned that the proportion of first-born children in Finland has gradually increased from 31 per cent in 1950 to 47 per cent in 1968 The age of the mothers, excluding children with Down's syndrome, did not significantly differ from the maternal age in general in Finland (115).

Birth weight and condition after birth. Table 3 shows that 24 per cent of the patients had a low birth weight of 2,500 g or less. Approximately 5 per cent of all children born alive in Finland during the same period of time belonged to this weight group. It may be mentioned that 100 of the 252 patients in the present study who died during the first week of life had a birth weight of 2,500 g or less 49 of them weighed less than 2,000 g The lowest birth weight was 800 g Table 3 shows that a low birth weight was less common in the patients with transposition of the great vessels than in the other groups of patients.

Forty-six per cent of the patients were asphyctic

Table 4 *Distribution of weights of the patients at death (A) compared with that of normal Finnish children of corresponding age (B). Figures given as percentages*

	Weight percentile position				
Under 2.5	2.5−16	16−50	50−84	84−97.5	Over 97.5
A. 57	19	13	6	3	2
B. 2.5	13.5	34	34	13.5	2.5

at birth (Table 3) The degree of asphyxia varied according to the Apgar scoring system, employed in Finland since 1954 from 0 to 7 The corresponding overall incidence of birth asphyxia in Finland is approximately 8 times less (65). The asphyxia was graded as slight, moderate or severe in cases in which the Apgar scoring system was not employed. Asphyxia occurred more often in patients with "cyanotic" heart lesions than in the other groups of patients. Extracardiac causes of asphyxia were common. Sixty per cent of the patients who died during the first week of life were asphyctic at birth. Birth asphyxia was more common in infants who died before 6 months of age (50 per cent) than in older patients (28 per cent)

Physical development and general condition A poor gain in weight was a common feature of the patients in the different groups. Table 4 shows the weight distribution of the patients at death compared with that of normal Finnish children of corresponding age (8, 130). The weight for age of the cardiac children was below the 16th percentile in 76 per cent of the cases whereas, of course, only 16 per cent of normal children belonged to this group. No less than 75 per cent of the patients with ventricular septal defects belonged to the lowest weight group (below the 2.5th percentile). Any comparison of the weights of patients with different types of congenital heart disease was hampered by the high incidence of various extracardiac causes for poor thriving

The general condition of the patients on admission to the hospital was classified as good or satisfactory in 18 poor in 57 and very poor in 25 per cent of the cases. The patients in the last group, most of whom were neonates, were usually moribund.

Cyanosis. Sixty per cent of the patients were cyanotic on clinical examination (Table 5). Cyanosis was more common in patients under 6 months of age (65 per cent) than in older infants and children (48 per cent). Congenital malformations of the heart are usually divided into acyanotic and cyanotic lesions. Patients with a predominantly left-to-right shunt usually belong to the former group. However cyanosis occurred in 33 per cent of the patients with ventricular septal defect. Cyanosis was also common in association with other septal defects and in patients without shunts. The reason for this, as will be seen, was the high incidence of extracardiac causes of cyanosis in these cases. Cyanosis was occasionally lacking in patients with "cyanotic" heart lesions. Only tricuspid atresia was invariably associated with cyanosis.

Table 5 *Incidence of cyanosis, cardiac failure pathological heart murmurs, and cardiomegaly in the different groups of patients. Figures given as percentages*

Main cardiac malformation	Cyanosis	Cardiac failure	Heart murmurs	Cardiomegaly
Endocardial fibroelastosis	19	82	37	82
Ventricular septal defect	33	37	50	52
Atrial septal defect	49	39	42	47
Combined septal defects	61	65	74	73
Patent ductus arteriosus	21	23	49	38
Coarctation of the aorta	47	64	43	58
Hypoplastic left heart syndrome	73	85	42	79
Transposition of the great vessels	96	80	56	72
Truncus arteriosus	89	62	47	54
Tetralogy of Fallot	89	20	84	47
Tricuspid atresia	100	68	68	50
Miscellaneous	45	55	42	71
Mean	60	57	51	61

Congestive heart failure Fifty-seven per cent of the patients showed signs of heart failure during hospitalization (Table 5) The main symptoms were: tachypnea at rest, difficulties in feeding, enlarged liver and heart and sometimes edema. Pulmonary rales and gallop rhythm were common findings. The incidence of cardiac failure was highest in patients with endocardial fibroelastosis, hypoplastic left heart syndrome and transposition of the great vessels. Cardiac failure was more common in patients under 6 months of age than in older patients. Cyanosis and cardiac failure were both lacking in 25 per cent of the conservatively treated patients, suggesting that the heart disease was not the main cause of death in many of these cases.

Heart murmurs. Fifty-one per cent of the patients revealed heart murmurs which were considered pathological (Table 5). The incidence of murmurs was 84 per cent in patients over 6 months of age, and 42 per cent in the younger infants. Pathological murmurs were heard during the first month of life in only one fifth of the patients with isolated ventricular or atrial septal defects and with patent ductus arteriosus. Only 10 per cent of the neonates under one week of age with ventricular septal defect revealed pathological heart murmurs. Murmurs were comparatively

Table 2. *Birth rank of the children in the present study (A) compared with that of 1,610,759 children born alive in Finland in 1950—1968 (B). Figures given as percentages*

	Birth rank							
	1	2	3	4	5	6	7	8—
A.	38	26	18	7	5	2	1	3
B.	36	26	16	9	5	3	2	3

A single vessel emerging from the heart and supplying the pulmonary and systemic circulation was the main feature of heart lesions classified as truncus arteriosus (75 cases). Whether some of the cases should have been classified as tetralogy of Fallot with pulmonary atresia or as hypoplastic left heart syndrome with aortic atresia was a matter of interpretation. Thirty of the patients had other cardiovascular anomalies in addition to a ventricular septal defect, which was present in all cases. There were 46 patients with tetralogy of Fallot; 11 of them had complicating cardiovascular anomalies. Tricuspid atresia was considered the main malformation in 22 cases. Associated anomalies were present in all cases.

A miscellaneous group (69 cases) mainly comprised valvular lesions and atresias (33 cases), anomalies of the venous return (13 cases), idiopathic congenital cardiac hypertrophy (10 cases) and isolated cases of Ebstein s malformation of the tricuspid valve, complete atrioventricular block, dextrocardia, anomalies of the coronary arteries, etc. Many of these miscellaneous anomalies were also encountered in the other groups of patients but they were not considered the main cardiac malformation. The incidence of different types of congenital heart disease did not significantly change during the course of the study

Sex The series comprised 439 boys and 338 girls (Table 1) Patients with coarctation of the aorta, hypoplastic left heart syndrome, transposition of the great vessels, truncus arteriosus, tetralogy of Fallot and tricuspid atresia showed a male preponderance, whereas patent ductus arteriosus was more common in girls than in boys. It may be mentioned that of the patients who died before 6 months of age, 59 per cent were boys and 41 per cent girls. There were, on the other hand, slightly fewer boys (48 per cent) that girls (52 per cent) among the patients over 6 months old

Age at death. Table 1 shows that 252 (32 per cent) of the patients were less than one week and 409 (53 per cent) less than one month of age. Death occurred during the first day of life in 127 (16 per

Table 3 *Percentage of low birth weight (2,500 g or less) and birth asphyxia*

Main cardiac malformation	Low birth weight	Birth asphyxia
Endocardial fibroelastosis	17	25
Ventricular septal defect	41	49
Atrial septal defect	33	35
Combined septal defects	23	50
Patent ductus arteriosus	19	28
Coarctation of the aorta	22	32
Hypoplastic left heart syndrom	25	35
Transposition of the great vessels	10	66
Truncus arteriosus	26	61
Tetralogy of Fallot	18	52
Tricuspid atresia	19	50
Miscellaneous	17	46
Mean.	24	46

cent) of the cases. The proportion of neonates did not significantly change during the course of the study Seventy-eight per cent of the patients died before 6 months of age and 86 per cent during the first year of life. Only 9 of the conservatively treated patients were over 10 years old. Table 1 shows that patients with hypoplastic left heart syndrome and with tricuspid atresia had a comparatively high early mortality

Birth rank and maternal age The order of birth of the patients compared with that of all children born alive in Finland from 1950 to 1968 is shown in Table 2. Thirty-eight per cent of the patients were the first born child. The order of birth did not differ from that of Finnish children in general. The birth rank showed a similar pattern for patients with different types of cardiac malformations. It may be mentioned that the proportion of first-born children in Finland has gradually increased from 31 per cent in 1950 to 47 per cent in 1968. The age of the mothers, excluding children with Down s syndrome, did not significantly differ from the maternal age in general in Finland (115).

Birth weight and condition after birth. Table 3 shows that 24 per cent of the patients had a low birth weight of 2,500 g or less. Approximately 5 per cent of all children born alive in Finland during the same period of time belonged to this weight group. It may be mentioned that 100 of the 252 patients in the present study who died during the first week of life had a birth weight of 2,500 g or less, 49 of them weighed less than 2,000 g. The lowest birth weight was 800 g Table 3 shows that a low birth weight was less common in the patients with transposition of the great vessels than in the other groups of patients.

Forty-six per cent of the patients were asphyctic

Table 7 *Percentage of children with extracardiac congenital malformations*

Main cardiac malformation	Single anomaly	Multiple nomalies	Total	Central nervous system	Alimentary system	Respiratory system	Genitourinary system	Skeleton, muscles, kin	Miscellaneous
Endocardial fibroelastosis	21	9	30	9	9	2	2	11	7
Ventricular septal defect	24	34	58	6	26	2	22	27	19
Atrial septal defect	25	27	[illegible]	6	18	9	16	[illegible]	18
Combined septal defects	35	39	74	2	26	8	10	18	57
Patent ductus arteriosus	36	23	59	8	29		1	19	8
Coarctation of the aorta	20	24	44	8	20	4	20	1	9
Hypoplastic left heart syndrome	21	15	36	6	15	6	10	4	8
Transposition of the great vessels	17	13	30	4	9	3	6	12	10
Truncus arteriosus	28	19	47	5	13	6	16	17	14
Tetralogy of Fallot	9	30	39	8	21	4	11	26	9
Tricuspid atresia	14	22	36	5	14	9	14	5	9
Miscellaneous	24	12	36	4	13	8	7	13	11
Mean	23	22	45	6	18	5	13	16	15

the lobes. A miscellaneous group included malformations of the larynx and trachea.

Ninety-nine patients had 115 malformations affecting the genitourinary organs, hydronephrosis and renal agenesis being the commonest anomalies (Table 6 D). Other urinary tract anomalies (40 lesions) included polycystic kidney renal hypoplasia, anomalies of the ureter vestibular anus, and isolated cases of malpositions, congenital nephrosis, strictures, etc. The genital organs were malformed in 11 boys and 8 girls.

Anomalies of the extremities and cleft palate were the commonest malformations confined to the skeleton, *muscles and skin* (Table 6 E). Eleven patients had clubbed feet and 5 had congenital dislocation of the hip. Other skeletal anomalies (50 lesions) affected the spine in 24 the skull in 17 and the ribs in 7 instances. Anomalies of the external ear were the commonest skin malformations.

There were 47 cases of Down's syndrome in the miscellaneous group of malformations (Table 6 F). Other anomalies (27 cases) included erythroblastosis fetalis (11 cases), anomalies of the thyreoidea (5 cases) and solitary cases of Turner's syndrome, chondrodystrophy Marfan's syndrome, defects of the thymus, congenital leukemia, etc.

Table 7 summarizes the occurrence of extracardiac congenital malformations in the different groups of cardiac anomalies. The incidence of these malformations was highest in patients with combined septal defects (74 per cent), patent ductus arteriosus (59 per cent) and ventricular septal defect (58 per cent). Septal defects were also associated with the highest density of extracardiac anomalies per case (1.0 to 1.5). The lowest incidence (30 per cent) was seen in patients with endocardial fibroelastosis and with transposition of the great vessels. These two cardiac anomalies were also associated with the lowest density of additional malformations (0.4 and 0.5). Table 7 shows the distribution of extracardiac anomalies in the different groups of heart lesions.

An accumulation of certain extracardiac anomalies occurred in patients with some specific heart lesions. Thus, 37 of the 47 cases of Down's syndrome were seen in patients with septal defects, in particular common atrioventricular canal. Only two patients with cyanotic heart lesions, one with tetralogy of Fallot, the other with transposition of the great vessels, revealed this syndrome. The highest incidence of esophageal atresia (12 per cent) was seen in patients with ventricular septal defect, whereas this anomaly occurred in only 3 per cent of the patients with coarctation of the aorta and with transposition of the great vessels. Septal defects were also comparatively more often associated with anomalies of the extremities (10 per cent), hydronephrosis (8 per cent) and with cleft palate (8 per cent) than other types of cardiac lesions. Situs inversus was seen only in patients with transposition of the great vessels, septal defects, tetralogy of Fallot and tricuspid atresia. These groups of cardiac lesions also included most of the cases of asplenia. The

Table 8 *Other causes of death Numbers of patients given in brackets*

	No.
A. Infections	No.
Pneumonia	424
Gastroenteritis	44
Carditis	20
Septicemia	13
Meningo-encephalitis	11
Peritonitis	10
Miscellaneous	11
Total	533 (457)
B. *Hemorrhages*	No.
Pulmonary	62
Intracranial	59
Other	16
Total:	137 (122)
C. *Thromboembolism*	No.
Intracranial	16
Pulmonary	7
Cardiac	6
Other	4
T tal:	33 (33)
D *Miscellaneous*	No
Pulmonary atelectases	54
Hyaline membrane disease	31
Cerebral lesions	16
Nephropathies	13
Other	23
Total:	137 (124)

incidence of multiple spleens was approximately the same in the different groups of cardiac anomalies.

Other causes of death. Contributory extracardiac causes of death, in addition to prematurity and malformations, were detected in 637 (82 per cent) of the patients. Infections of one or several organs occurred in 457 (59 per cent) of the patients (Table 8 A). The overall incidence of infections was highest in patients with endocardial fibroelastosis (77 per cent) and with transposition of the great vessels (77 per cent) and lowest in patients with hypoplastic left heart syndrome (43 per cent) and with tetralogy of Fallot (43 per cent). Pneumonia, which was confirmed microscopically in all cases, occurred in 424 (55 per cent) of the patients. This complication was more common in patients with pulmonary plethora than in the other groups of patients. Pneumonia was equally common in infants under 6 months of age and in older patients. Carditis occurred in 20 patients most of them showed diffuse inflammation of the heart or purulent pericarditis. Isolated endocarditis was present in only 5 instances. Carditis was rare in infants under 6 months of age. This complication was not seen in patients with atrial septal defect, hypoplastic left heart syndrome, tetralogy of Fallot or tricuspid atresia. Infections of the brain including abscesses, (11 cases), were more common in cyanotic than in acyanotic patients. Peritonitis and septicemia mainly occurred as complications to operations performed for congenital intestinal obstructions. A miscellaneous group of infections (11 cases) comprised nephritis, pancreatitis, hepatitis, etc. Infections have become less common causes of death during the course of the study

Hemorrhages in different organs were encountered in 122 (16 per cent) of the patients (Table 8 B). Pulmonary and intracranial hemorrhages were the commonest varieties. A miscellaneous group (16 cases) comprised hemorrhages in abdominal organs and hemolytic disease of the newborn. The incidence of hemorrhages was highest in patients with hypoplastic left heart syndrome (26 per cent) and with coarctation of the aorta (22 per cent), and lowest in association with tetralogy of Fallot (4 per cent) and tricuspid atresia (4 per cent). Patients with coarctation of the aorta and with hypoplastic left heart syndrome had the highest incidence of intracranial hemorrhage (12 and 14 per cent) Hemorrhages occurred more often in infants under 6 months of age than in older patients.

Thromboembolism was detected in 33 (4 per cent) of all cases (Table 8 C). This complication was comparatively common in patients with tetralogy of Fallot (13 per cent) and transposition of the great vessels (11 per cent) and rare in acyanotic cases. Patients over 6 months of age were more often affected than younger infants. Coronary thrombosis was seen in 6 patients 3 of them had hypoplastic left heart syndrome. A miscellaneous group comprised thromboembolism in abdominal organs and in the limbs.

Miscellaneous causes of death occurred in 124 (16 per cent) of the cases (Table 8 D). Pulmonary atelectases and hyaline membrane disease were the commonest findings. The highest incidence of both these lesions was seen in patients with septal defects (8 to 26 per cent) and the lowest in patients with tricuspid atresia (nil) and tetralogy of Fallot (2 per cent) Pulmonary atelectases occurred in 9 per cent of infants under 6 months of age and in 0.6 per cent of older patients. Brain lesions were seen in 16 cases and acquired nephropathies occurred in 13 instances. Other diseases (23 cases) comprised malabsorption, blood diseases, nephrosis, cardiomyopathies, tumors, cirrhosis of the liver ileus, etc.

An analysis of the data showed that extracardiac disorders, including prematurity congenital malformations and diseases of the newborn, were primary or contributory causes of death in 90 per cent

Table 9 *Postoperative deaths*

Main cardiac malformation	No. of patients	Heart operations Age Under 1 yr	1–5 yrs	5–10 yrs	10–16 yrs	Other operations No. of patients
Endocardial fibroelastosis						1
Ventricular septal defect	10	4	2	2	2	15
Atrial septal defect						7
Combined septal defects	3	1	1		1	6
Patent ductus arteriosus	9	2	1	2	4	14
Coarctation of the aorta	9	4	1	3	1	12
Hypoplastic left heart syndrome	5	4	1			2
Transposition of the great vessels	15	9	5	1		6
Truncus arteriosus	4	3	1			7
Tetralogy f Fallot	15	5	2	6	2	12
Tricuspid atresia	1	1				2
Miscellaneous	11	6	1	1	3	10
Total:	82	39	15	15	13	94

of the conservatively treated patients. Most infections and some of the vascular complications were considered secondary causes of death.

Postoperative deaths Eighty-two patients, 39 of whom were under one year of age, underwent car diac surgery (Table 9). Palliative operations were performed in 44 cases and corrective surgery was carried out in 33 Explorative thoracotomy was per formed in 5 cases. Twenty of the patients with left to-right shunts had severe pulmonary hypertension. In 32 cases the death could be explained by the presence of extracardiac pathology and complicating cardiac lesions, which in all probability were not compatible with longevity Heart failure was the commonest immediate cause of death. Postoperative hemorrhages occurred in 15 and thromboembolism in 10 cases. Infections were causes of death in 3 cases. Twelve of the patients had extracardiac congenital malformations.

An additional 94 patients underwent surgery mainly for extracardiac congenital malformations (Table 9). Forty-five of the patients were under one week of age and 80 were less than 6 months old. The commonest anomalies were: esophageal atresia (32 cases), intestinal obstructions (30 cases), omphalocele (10 cases) and diaphragmatic hernia (6 cases).

Diagnostic errors The heart disease was recognized during lif in 71 per cent of the cases (Table 10). Errors were especially common in newborns under one week of age. Thus, the heart disease was an "autopsy surprise" in no less than 61 per cent of the infants in this age group. Isolated septal defects and patent ductus arteriosus were more often overlooked in young infants than complicated heart lesions. These two anomalies were recognized in only 18 and 7 per cent of the infants less than one week of age. Table 10 shows that diagnostic errors were rarer in patients with cyanotic congenital heart disease and in older infants and children. Thus, the heart disease was detected during life in 150 of 168 patients over 6 months and in 103 of 110 children over one year of age. Our ability to recognize congenital heart disease in neonates and young infants in the present series did not significantly improve during the course of the years. Thus, the heart disease was detected during life in 68 per cent of the 308 patients studied from 1947 to 1957 whereas the corresponding figure was 73 per cent for 469 patients seen after 1957 It may be mentioned that a large proportion of the cardiac children were primarily admitted to the hospital for other reasons, such as prematurity noncardiac malformations and various diseases of the newborn.

Length of hospitalization. Sixty-one per cent of the patients died within week of admission to the hospital. One third died during the first day of hospitalization. Patients with endocardial fibroelastosis and with transposition of the great vessels showed the highest early mortality Death occurred one week to one month after admission in 29 per cent of the cases. Only 78 (10 per cent) of the pa tients were hospitalized for more than one month.

Operability Could death have been prevented by means of cardiac operation in conservatively treated cases? Considering the heart disease only many of the anomalies would have been amenable to palliative and some also to corrective surgery However the heart disease was considered an incidental finding and in all probability irrelevant to the cause of death in one fourth of the cases. Patients with septal defects in particular belonged to this group. Cardiac

Table 8. *Other causes of death Numbers of patients given in brackets*

A. Infections	No
Pneumonia	424
Gastroenteritis	44
Carditis	20
Septicemia	13
Meningo-encephalitis	11
Peritonitis	10
Miscellaneous	11
	Total. 533 (457)
B. *Hemorrhages*	No.
Pulmonary	6[illegible]
Intracranial	59
Other	16
	Total: 137 (122)
C. *Thromboembolism*	No.
Intracranial	16
Pulmonary	7
Cardiac	6
Other	4
	Total. 33 (33)
D *Miscellaneous*	No
Pulmonary atelectases	54
Hyaline membrane disease	31
Cerebral lesions	16
Nephropathies	13
Other	23
	Total: 137 (124)

incidence of multiple spleens was approximately the same in the different groups of cardiac anomalies

Other causes of death Contributory extracardiac causes of death, in addition to prematurity and malformations, were detected in 637 (82 per cent) of the patients. Infections of one or several organs occurred in 457 (59 per cent) of the patients (Table 8 A). The overall incidence of infections was highest in patients with endocardial fibroelastosis (77 per cent) and with transposition of the great vessels (77 per cent) and lowest in patients with hypoplastic left heart syndrome (43 per cent) and with tetralogy of Fallot (43 per cent). Pneumonia which was confirmed microscopically in all cases, occurred in 424 (55 per cent) of the patients. This complication was more common in patients with pulmonary plethora than in the other groups of patients. Pneumonia was equally common in infants under 6 months of age and in older patients. Carditis occurred in 20 patients most of them showed diffuse inflammation of the heart or purulent pericarditis. Isolated endocarditis was present in only 5 instances. Carditis was rare in infants under 6 months of age. This complication was not seen in patients with atrial septal defect, hypoplastic left heart syndrome, tetralogy of Fallot or tricuspid atresia. Infections of the brain, including abscesses, (11 cases), were more common in cyanotic than in acyanotic patients. Peritonitis and septicemia mainly occurred as complications to operations performed for congenital intestinal obstructions. A miscellaneous group of infections (11 cases) comprised nephritis, pancreatitis, hepatitis, etc. Infections have become less common causes of death during the course of the study

Hemorrhages in different organs were encountered in 122 (16 per cent) of the patients (Table 8 B). Pulmonary and intracranial hemorrhages were the commonest varieties. A miscellaneous group (16 cases) comprised hemorrhages in abdominal organs and hemolytic disease of the newborn. The incidence of hemorrhages was highest in patients with hypoplastic left heart syndrome (26 per cent) and with coarctation of the aorta (22 per cent), and lowest in association with tetralogy of Fallot (4 per cent) and tricuspid atresia (4 per cent). Patients with coarctation of the aorta and with hypoplastic left heart syndrome had the highest incidence of intracranial hemorrhage (12 and 14 per cent) Hemorrhages occurred more often in infants under 6 months of age than in older patients.

Thromboembolism was detected in 33 (4 per cent) of all cases (Table 8 C). This complication was comparatively common in patients with tetralogy of Fallot (13 per cent) and transposition of the great vessels (11 per cent) and rare in acyanotic cases. Patients over 6 months of age were more often affected than younger infants. Coronary thrombosis was seen in 6 patients 3 of them had hypoplastic left heart syndrome A miscellaneous group comprised thromboembolism in abdominal organs and in the limbs.

Miscellaneous causes of death occurred in 124 (16 per cent) of the cases (Table 8 D). Pulmonary atelectases and hyaline membrane disease were the commonest findings. The highest incidence of both these lesions was seen in patients with septal defects (8 to 26 per cent) and the lowest in patients with tricuspid atresia (nil) and tetralogy of Fallot (2 per cent). Pulmonary atelectases occurred in 9 per cent of infants under 6 months of age and in 0.6 per cent of older patients. Brain lesions were seen in 16 cases and acquired nephropathies occurred in 13 instances. Other diseases (23 cases) comprised malabsorption, blood diseases, nephrosis, cardiomyopathies, tumors, cirrhosis of the liver ileus, etc.

An analysis of the data showed that extracardiac disorders, including prematurity congenital malformations and diseases of the newborn, were primary or contributory causes of death in 90 per cent

DISCUSSION

Incidence of congenital heart disease in autopsy series There is no evidence that the incidence of congenital heart disease in Finland has significantly changed during the past two decades. The relative increase of these lesions seen in the present autopsy series appears to be largely due to the fact that other diseases, infections in particular have become less common causes of death in children than in the past. Moreover since the advent of heart surgery an increasing number of cardiac patients have been referred for treatment to the Children s Hospital in Helsinki. Similar studies have been published according to which the role played by congenital heart disease in child mortality has increased during the past few decades (59 71 145).

The incidence of congenital heart disease varies considerably in published autopsy series depending on the age of the patients and methods of selection employed. Fontana and Ewards (45) found congenital cardiac defects in only 1.2 per cent of autopsies performed on 22,361 patients of all ages. The incidence of heart malformations in some autopsy series consisting of infants and young children varies from 5 to 16 per cent (46, 75 79 84 146). In a review of death certificates of infants under one year of age, Allen (5) stated that congenital heart disease accounted for death in 7 6 per cent of the cases.

Accurate appraisal of the incidence of different types of congenital heart disease in autopsy series is difficult, because published data are not readily comparable. There are also reports suggesting geographical differences in the prevalence of certain cardiac anomalies. Thus, coarctation of the aorta and aortic stenosis have been found to be comparatively rare (50 66, 110, 127), whereas truncus arteriosus is reported to be common (140) in some Asian countries. A source of error to be considered in comparing incidence studies is that complicated anomalies of the heart may be interpreted and, hence, classified differently by different observers. Truncus arteriosus, for example, can easily be confused with tetralogy of Fallot with pulmonary atresia or with hypoplastic left heart syndrome with aortic atresia because of the many hemodynamic and anatomical features these three syndromes have in common (53). Moreover comparison of incidence studies in congenital heart disease is hampered by differences in the nomenclature employed.

The present series is in agreement with previous autopsy studies on young infants and children with congenital heart disease according to which septal defects, coarctation of the aorta, transposition of the great vessels and hypoplastic left heart syndrome are the commonest anomalies (15 31 69 70 99 122). Cases classified as truncus arteriosus were comparatively common in the present series but the proportion of newborns and young infants was much higher than in most previously published autopsy studies. In young infants truncus arteriosus has been found to be more common than for example tetralogy of Fallot (5, 136). The incidence of endocardial fibroelastosis corresponded by and large to that reported in other autopsy studies on cardiac infants and children (46, 74 122). Most of the patients with coarctation of the aorta had additional cardiovascular anomalies, which supports observations made by previous investigators (69 128 142). In a post-mortem study of 46 young infants with coarctation of the aorta, Malm and Blumenthal (93) found additional cardiovascular anomalies in 44 of the cases. The present study is also in agreement with reports according to which isolated aortic stenosis (75 122) and Ebstein s anomaly (125) are rarely encountered in autopsies on infants and young children.

Sex, birth rank and birth weight Children with congenital heart disease usually show an overall male preponderance (5 6, 28, 45 101). In the present study this sex difference was greater in patients under 6 months of age than in the older infants and children. It may be mentioned that a male preponderance has been observed in all infants dying during the first year of life in Finland (82). Some clinical series, mainly consisting of adult patients with congenital heart disease, have revealed an even sex distribution (129). The present study supports observations according to which coarctation of the aorta (25, 45 48, 69 134), transposition of the great vessels (3 24 69 89 111), and tetralogy of Fallot (24 69 89 122) are more common in boys than in girls, whereas patent ductus arteriosus usually shows a female preponderance (24 41 53, 69 72).

The patients did not differ from Finnish children in general with regard to the order of birth and the age of the mother an observation which has been made in some previous studies (23 28, 95, 117 141). However a positive correlation has also been reported between advanced maternal age and the incidence of congenital heart disease in children (60, 101 118)

Congenital heart defects have been found to be more common in premature than in fullterm babies (28, 64 94 101 118 141). However a comparatively low incidence of prematurity has also been reported

in infants with congenital heart disease (5) It has been suggested that retarded intrauterine growth rather than reduced gestational age is responsible for the low birth weight of cardiac children (103) One fourth of the patients in the present study had a low birth weight of 2,500 g or less, an incidence approximately 5 times higher than for Finnish children in general. It is difficult to say whether the low birth weight in these cases was due to the heart defects or whether prematurity was a predisposing factor for these malformations. The observation that patients with transposition of the great vessels had a comparatively high birth weight is in agreement with previous reports (97 103).

Mortality In a carefully planned prospective study of 116, 419 children born in Gothenburg during the period 1941 to 1960, Carlgren (26, 27 28) found congenital heart disease in 838 cases, an incidence of approximately 0 8 per cent of liveborn infants. Thirty-four per cent of the cardiac children died during the follow-up period, which varied from 8 to 28 years. There were 17 postoperative deaths. Twenty per cent of the patients died during the first year of life, the mortality being highest in the neonatal period. A similar age distribution was seen among the patients in the present study and also in previous reports on the mortality and age at death of children with congenital heart disease (6, 15 46, 146). In the present series, very few patients with complicated cardiac defects were over one year of age. There are, however reports on patients with severe heart anomalies such as truncus arteriosus (39 52, 53), hypoplastic left heart syndrome (53) and tricuspid atresia (29 34) who have survived to adulthood. Similar cases have been seen att the Children s Hospital in Helsinki. Uncomplicated septal defects, on the other hand, have rarely been considered the main cause of death in young infants (2, 63 68 69 99 104).

Extracardiac congenital malformations Studies on the occurrence and nature of multiple malformations may throw additional light on the pathogenesis of these lesions. It has been suggested that a teratogenic agent may act adversely on several points in the embryo, giving rise to multiple anomalies, or that one defect can induce a sequence of events resulting in several defects (40 131). Extracardiac malformations occurred in 45 per cent of the patients in the present series. In a post-mortem study of 1 145 children under 4 years of age with congenital heart disease, Boesen and his associates (17) found additional anomalies in 23 per cent of the cases. The incidence of noncardiac anomalies in other clinical and autops studies of children with congen tal heart disease varies from 14 to 48 per cent (12, 55 56 70, 75 108 1__ 147) Conversely cardiac malformations have been reported to be common in patients with anomalies of other vital organs (21 44 106, 138)

There was a high association of Down s syndrome with septal defects, particularly with common atrioventricular canal. The same observation has been made by other investigators (9 36, 42, 58, 91 114 121 141). Only very few patients with cyanotic heart disease revealed this syndrome in the present series. Septal defects were also associated with the highest incidence of other noncardiac anomalies. Moreover an accumulation of certain malformations such as esophageal atresia, hydronephrosis and cleft palate were seen in association with septal defects. Some authors have observed a high overall incidence of extracardiac anomalies in patients with septal defects (108 122) but a comparatively low incidence has also been reported in some clinical series (28). Most studies have so far failed to show any specific pattern of extracardiac anomalies in different types of congenital heart disease (6, 17 101 144). The present study supports the view that asplenia is comparatively often associated with complicated malformations of the heart (67 122), whereas multiple spleens are equally common in patients with different types of heart anomalies (119). Our knowledge of the pathogenesis of congenital malformations is still too fragmentary to permit conclusions as to the reason for an accumulation of extracardiac anomalies in children with certain types of heart defects.

Other causes of death. Several authors have commented on the frequent occurrence of complicating diseases, infections in particular in children with congenital heart disease (6, 28 46, 61 69 88, 93). In an autopsy study of 31 newborn infants with ventricular septal defect, Mehrizi and his associates (99) found extracardiac causes of death in 29 cases. The present study also supports the view that pulmonary complications are more common in patients with increased than in those with decreased pulmonary flow (69 112). There are previous reports on the occasional occurrence of brain abscesses particularly in cyanotic cardiac children (35 45 131).

Bacterial endocarditis seems to be rare in young infants with congenital heart disease (14 54 69) but the risk has been found to increase with age (37 45). Hemorrhages in various organs, even in newborns, were comparatively common in patients with obstructive lesions of the aorta, whereas thromboembolism occurred more often in cyanotic than in acyanotic patients. Similar observations have been made in previous studies (80, 131 133). Gross coronary thrombosis was seen in 6 cases. A higher incidence of cardiac infarction has been reported in

microscopic studies on infants with congenital heart disease, particularly in association with anomalous origin of the coronary arteries (43 47 124).

Diagnostic problems. It is generally agreed that recognition of congenital cardiac anomalies is difficult in newborns and young infants. Symptoms and signs of cardiac involvement are often lacking. Auscultatory findings are frequently normal (19 46, 135) and routine X-ray may be of only limited value (7 51 126). Moreover a variety of extracardiac disorders, most of them of pulmonary or cerebral origin, have been found to give rise to symptoms and signs simulating heart disease (75 85 86, 88 105 120). In a study of 93 cyanotic newborn babies, Graig (57) found congenital heart disease in only 14 cases various other diseases, such as intracranial lesions and pulmonary disorders, were the cause of cyanosis in the remainder of the cases. Review of this topic shows that congestive heart failure in the absence of primary cardiac disease is not rare in the neonatal period. Asphyxia at birth (22), anemia (87) and placental transfusion syndrome (87 116) have been found to be causes of cardiomegaly and heart failure in newborns.

The present study supports previous reports according to which congenital malformations of the heart are frequently overlooked in newborns and young infants (10, 49, 51 53 62, 70 88, 101). It should also be remembered that many of the new born babies died soon after admission to the hospital without there having been possibilities for further cardiac studies. Nor were detailed cardiac studies carried out on most of the infants admitted for emergency operations for extracardiac malformat ions.

In a follow-up study of 838 children with congenital heart disease, Carlgren (26, 27 28) stated that the defect was recognized in the neonatal period in 20 per cent of the cases. Moreover he found no close correlation between the severity of the heart disease and the age of the children when the lesion was detected. A co-operative study from Denmark showed that 264 of 464 cases of tetralogy of Fallot were diagnosed after the second year of life (148). In a series comprising 200 school children with congenital heart disease admitted for operation to the Children's Hospital in Helsinki, the defect was detected during the first year in 67 cases (83).

Therapeutic aspects. There seems at present to be a fairly general attitude favouring an aggressive policy in the management of newborns and young infants with congenital heart disease. Such an approach seems justified in view of the fact that fatalities among cardiac children are so common during the first months of life. What are the possibilities of successful cardiac surgery at this age? It is fully realized that the present series comprised highly selected and severe cases. Nevertheless, the study clearly showed the many therapeutic problems presented by critically ill cardiac infants. Some of these problems seem to deserve brief comment.

Evidence was presented that cardiac surgery might have been performed with a reasonable hope of success and long-term survival on only a small proportion of the conservatively treated neonates and young infants in the present series. On the other hand, it may be argued that an aggressive therapeutic approach would still have been justified since the patients were lost anyway

Accurate diagnosis of congenital heart defects, particularly in young infants, usually necessitates complete studies including cardiac catheterization and/or angiocardiography These investigations are not without risk in sick neonates and infants. Co-operative studies have shown a mortality rate of 6 per cent in association with heart catheterization in cardiac infants under two months of age (20). Even higher mortality rates (10 to ₋5 per cent) have been reported following complete cardiac studies in sick infants (3₋, 73 75 89 136, 137). A very active diagnostic approach at this early stage may therefore, lead to the loss of cardiac infants who could have survived to an age when the risks of these investigations are much less. Advances made in the medical treatment of infants with congenital heart disease have also considerably improved the outlook for these patients (6, 18, 31). Beuren (11) reported that the mortality among hospitalized children with congenital heart disease under one year of age decreased from 70 per cent in 1959 to 20 per cent in 1969 The frequent occurrence of spontaneous closure of ventricular septal defects during early infancy (13 18, 64 109 122) also favours conservative treatment in many of these cases.

The high risks of heart operations performed during the first months of life should also be taken into consideration in planning the treatment in individual cases. Up to 1971 1,696 children with congenital heart disease were operated upon at the Children's Hospital in Helsinki. In addition, 25 infants with transposition of the great vessels underwent Rashkind's balloon septostomy with 10 deaths. Open-heart surgery was performed in 350 cases. Pulmonary artery banding was carried out on 26 infants. The overall operative mortality was 5.2 per cent. However the mortality was 27 per cent in 144 patients under one year of age and 57 per cent for infants less than 6 weeks old (92). Moreover preoperative evaluation of the heart defect proved to be misleading or wrong in 10 per cent of the infants under 6 months of age, whereas diagnostic errors were rare in older children. Equally high

mortality rates in heart operations performed during the first months of life have been reported from other centers (11 33 38 73 90 136). The frequent occurrence of re-stenosis after surgical correction of coarctation of the aorta performed during the first months of life (142) should also be taken into consideration in planning the treatment of these patients. It may be mentioned that many of the older cardiac children successfully operated upon at the Children s Hospital in Helsinki were in severe heart failure and distress during early infancy Moreover severe extracardiac malformations were rare in patients over one year of age.

Many factors have to be considered in planning the treatment of neonates and young infants with congenital heart disease. It should be remembered that the majority of children with operable congenital heart disease survive the first six months of life. Except for patients with certain lesions, such as transposition of the great vessels, it seems that little can be done for most cardiac children succumbing in the neonatal period or early infancy because of the high incidence of primary extracardiac causes of death or the severity of the heart disease. But needless to say early cardiac surgery may be life-saving in individual cases. Many gratifying long-term results of palliative and corrective cardiac operations performed on young infants have been seen at our hospital in recent years. However the difficulties in selecting the right candidates for early surgery are appreciated by most pediatric cardiologists. It is to be hoped that further experience in the medical and surgical treatment of neonates and young infants with congenital heart disease will render the task easier

SUMMARY

The series comprised 777 children with congenital heart disease studied clinically and post-mortem at the Children s Hospital in Helsinki during the period 1947 to 1970. The incidence of cardiac malformations in 5 697 consecutive autopsies increased from 4.6 per cent in 1947 to over 20 per cent in recent years. Information about the cardiac patients was collected from the autopsy protocols and from the clinical notes made on the patients during hospitalization. Using a coding system, 34 main clinical and morphological data were recorded in each case. A total of approximately 30 000 items of information were obtained and analyzed by computer

There were 439 boys and 338 girls. One third of the children were less than one week and half were under one month of age. Death occurred during the first year of life in 86 per cent of the cases. Only 9 of the conservatively treated patients were over 10 years old.

The main cardiac anomalies were, in decreasing order of frequency isolated and combined septal defects (226 cases), transposition of the great vessels (102 cases), truncus arteriosus (75 cases), coarctation of the aorta (74 cases), hypoplastic left heart syndrome (72 cases), isolated patent ductus arteriosus (47 cases), tetralogy of Fallot (46 cases), endocardial fibroelastosis (44 cases) and tricuspid atresia (22 cases). Miscellaneous cardiovascular anomalies were present in 69 cases. In many of the complicated cases the classification was based on hemodynamic rather than on strictly anatomical criteria. Some groups of complicated heart anomalies overlapped.

The patients did not differ significantly from Finnish children in general with regard to the order of birth and the age of the mother Sex differences were seen in some groups of cardiac lesions. The birth rank showed a similar pattern for children with different types of heart lesions. One fourth of the children had a low birth weight of 2,500 g or less. Asphyxia at birth occurred in 46 per cent of the cases.

A poor physical development was the commonest single feature of the patients. Their weight for age at death was below the 16th percentile in 76 per cent of the cases. The general condition of the patients on admission was poor in 82 per cent of the cases. Two thirds of the patients died within one week of hospitalization, one third during the first day

Clinical signs of heart disease were lacking in one fourth of the patients. Sixty per cent of the children were cyanotic. Extracardiac diseases, mostly of pulmonary or cerebral origin, were common causes of cyanosis. Congestive heart failure occurred in 57 per cent of the cases. Only half of the patients revealed pathological murmurs. Heart murmurs were lacking in the vast majority of the patients under one month of age with ventricular septal defects and with patent ductus arteriosus. Cardiac enlargement and/or hypertrophy occurred in 61 per cent of the cases.

Extracardiac congenital malformations were present in 45 per cent of the cases. Half these patients had multiple anomalies. There was no significant correlation between the incidence of noncardiac malformations and the order of birth. The overall incidence of these anomalies was the same for boys and girls but certain malformations showed sex differences. Most of the associated malformations were confined to the alimentary tract (138 cases) the skeleton, muscles and skin (124 cases) and the genitourinary tract (99 cases). Forty-seven children had Down s syndrome. The highest incidence of noncardiac malformations was seen in patients with septal defects. An accumulation of some defined anomalies was seen in patients with certain heart lesions. Extracardiac malformations of clinical significance were rare in patients over one year of age.

Various other diseases, mostly infections, were diagnosed in 82 per cent of the cases. Half of the patients had pneumonia. This complication was most common in patients with pulmonary plethora. Isolated endocarditis was seen in only 5 cases. Brain abscesses were more common in cyanotic than in acyanotic patients. The incidence of hemorrhages in different organs (122 cases) was highest in patients with obstructive lesions of the aorta. Thromboembolism (33 cases) usually occurred in cyanotic patients. Other diseases (124 cases) mainly included pulmonary atelectases and hyaline membrane disease.

Cardiac operations were performed on 82 patients, half of whom were infants under one year of age. In addition, 94 patients underwent operations, most of them for extracardiac congenital malformations. The overall mortality in 1 696 heart operations performed at the hospital was 5.2 per cent. The mortality was 27 per cent in infants under one year of age and 57 per cent for infants less than 6 weeks old.

A large proportion of the patients were primarily admitted to the hospital for disorders such as prematurity noncardiac malformations and various diseases of the newborn. The heart disease was recognized during life in 71 per cent of the cases.

ACKNOWLEDGEMENTS

The clinical part of this study was based on observations made by several pediatricians and pediatric cardiologists working at the Children's Hospital in Helsinki during the period 1947 to 1970 I want to express my appreciation to these persons, too numerous to mention individually for their valuable contributions. Particular thanks are due to my associate at the department of cardiology of the hospital Ass. Prof Leena Tuuteri, M.D for her help in collecting the clinical material.

The study would not have been possible without the work done by the staff at the department of pathology of the hospital. The following pathologists were heads of this department during the afore mentioned period. Prof E. K. Ahvenainen, M.D (1948–1954), Assoc. Prof L. Hjelt, M.D (1954–1968) and Ass. Prof. M H. J Rapola, M D (1968–). Much credit should go to them and to their associates for having performed the autopsies and for kindly placing their protocols and material at my disposal.

I also wish to record my gratitude to former and present cardiac surgeons at the department of surgery of the hospital (Head: Prof M Sulamaa, M.D) for their valuable contribution to this study

Ass. Prof. Riitta Liisa Kantero M.D was of great help in planning the coding system. The results were analyzed at the Computing Centre of the University of Helsinki. Some data were obtained from the Central Statistical Office in Helsinki.

The study was aided by a grant from the Sigrid Jusélius Foundation in Helsinki.

Helsinki, May 1971.

Bernhard Landtman

41 Ekström, G The surgical treatment of patent ductus arteriosus. A clinical study of 290 cases. *Acta Chir Scand*, suppl. 169 1952.

42. Esen, F M Congenital heart malformations in mongolism with special reference to ostium atrio-ventriculare commune. *Arch Pediat 74* 277 1957

43 Esterly J R. & Oppenheimer E. H. Some aspects of cardiac pathology in infancy and childhood. IV Myocardial and coronary lesions in cardiac malformations. *Pediatrics, 39*·896, 1967

44 Fonkalsrud, E. W De Lorimier A. A. & Hays, D M Congenital tresia and stenosis of the duodenum. A review compiled from the members of the surgical sections of the American Academy of Pediatrics. *Pediatrics, 43* 79 1969

45 Fontana, R. S. & Edwards, J E. *Congenital cardiac disease A review of 357 cases studied pathologically* Saunders, Philadelphia 1962.

46. Forfar J O Miller R. A., Bain, A. D & Macleod, W Endocardial fibroelastosis. *Brit Med J* 2 7 1964

47 Franciosi, R. A. & Blanc, W A. Myocardial infarcts in infants and children. I. A necropsy study in congenital heart disease. *J Pediat 73* 309, 1968.

48. Frederiksen, T Coarctation of the aorta (A genetic study). *Acta Genet (Basel), 13* 263 1963

49 Freire-Maia, N & Arce-Gomez, B. Epidemiological studies in congenital heart disease. VI World Congress of Cardiology London, September 1970, Abstracts p. 44

50. Furuta, S. Phonocardiogram in congenital heart disease. *Jap Circ J 25* 8, 1961

51 Fyler D C. Diagnosis and treatment: The salvage of critically ill newborn infants with congenital heart disease. *Pediatrics 42* 198, 1968

52. Garcia, R., Cargill, J W & Drake, E. H. Pseudotruncus arteriosus. Report of the oldest surviving patient. *Amer Heart J 78* 537 1969

53 Gasul, B. M Arcilla, R. A. & Lev M. *Heart disease in children. Diagnosis and treatment.* Lippincott, London-Philadelphia 1966.

54. Gelfman, R. & Levine, S. A. The incidence of acute and subacute bacterial endocarditis in congenital heart disease. *Amer J Med Sci 204* 324 194..

55 Gibson, W M. A survey of the post-mortem findings in 200 cases of congenital heart disease. *Gr Ormond Str J 11*·68 1956.

56. G bson, S. & Clifton, W M. Congenital heart disease. *Amer J Dis Child, 55* 761 1938.

57 Graig, W S. Admissions and re-admissions from districts to the special baby care unit f mater nity hospital. *Brit Med J* 2 1139 1962.

58 Grölkinger, H. & Schmid, F Das Mongolismus Herzsyndrom. *Z Kreislaufforsch 47* 164 1958.

59 Hackensellner H. A. Missbildungen des Herzens und der grossen Gefässe unter 25 467 Obduktionen. *Klin Med (Wien), 14*·61 1959

60. Harvald, B. & Hels, J The incidence of cardiac malformations in Greenlandic Eskimos. *Acta Med Scand, 185*·41 1969

61 Hastreiter A. R. Endocardial fibroelastosis. In A. J Moss & F H. Adams (eds.): *Heart disease in infants, children and adolescents.* Williams & Wilkins, Baltimore 1968, p 760.

62. Higgins, I. T T The epidemiology of congenital heart disease. *J Chronic Dis, 18*·699 1965

63 Hoffman, J I. E. N tural history of congenital heart disease. Problems in its assessment with special reference to ventricular septal defects. *Circulation, 37*·97 1968

64. Hoffman, J I E. & Rudolph, A. M The natural history of entricular septal defects in infancy *Amer J Cardiol 16*·634 1965

65. Ikonen, R. S. The Apgar scoring of newborn infants and its relation to neonatal mortality *Ann Paediat Fenn, 13* 111 1967

66. Imperial, E. S. & Felarca, A. Autopsy study f heart disease in the Philippines General Hospital: Based on review of 6000 consecutiv cases. *Amer Heart J 66*·470 1963

67 I emark, B. I Implication of agenesis of the spleen on the pathogenesis of cono-truncus anomalies in childhood: An analysis of the heart malformations in the splenic agenesis syndrome, with fourteen new cases. *A ta Paediat Scand,* suppl 104 1955

68 Kaplan, S., Daoud, G L, Benzing, G Devine, F J Glass, I H & McGuire, J Natural history of ventricular septal defect. *Amer J Dis Child, 105* 581 1963

69 Keith, J D., Rowe, R. D & Vlad, P *Heart disease in infancy nd childhood.* The MacMillan Co, New Y rk London 1966.

70. Kerl, H. Zur Häufigkeit und Korrelation kongenitaler A giocardiopathien. Eine Analyse von 530 obduzierten Herz-Gefäss-Missbildungen, *Z Kreislaufforsch, 58* 546, 1969

71 Kerrebijn, K. F Incidence in infants and mor tality from co genital malformations of the cir culatory system. *Acta Paediat Scand, 55* 316, 1966.

72. Krovetz, L. J & Warden, H. E. Patent ductus arteriosus. An analysis f 515 surgically proved cases. *Dis Chest, 42* 46, 1962.

73 Krovetz, L. J Shanklin, D R. & Schiebler G L. Serious and f tal complications of catheterization and angiocardiography in infants and children. *Amer Heart J 76* 39 1968.

74 Lambert, E. C., Schumway C. N & Terplan, K. Clinical diagnosis f endocardial fibrosis. Analysis of literature with report of four new cases. *Pediatrics, 11* 253 1953

75 Lambert, E. C., Canent, R. V & Hohn, A. R. Congenital cardiac anomalies in the newborn. A review of conditions causing death or severe distress in the first month of life. *Pediatrics, 37* 343 1966

76. Lamy M. & Schweisguth, O Enquete etiologique sur 304 malformations cardiques congenitales. *Ann Pediat (Paris), 174*·65 1950.

77 Landtman, B. Aetiology of congenital heart disease. Epidemiological aspects. Proc of the Vth Europ Congress of Cardiol. Athens, September 1968, p. 3.3

78. Landtman, B. The fifth Edgar Mannheimer memorial lecture. Clinical and morphological aspects of congenital heart disease. Proc Assoc Europ Paediat Cardiol, 7 2 1971

79 Landtman, B & Hjelt, L. Congenital heart disease. A clinical and post mortem study of 246 cases. *Ann Paediat Fenn, 5* 139 1959

80. Landtman, B. & Tuuteri, L. Vascular complications in coarctation of the aorta. *Acta Paediat Scand, 48* 329 1959

81 Landtman, B., Närvänen, S., Pasila, M., Sulamaa, M., Suutarinen, T & Tuuteri, L. Results of 1000 cardiac operations in children. *Duodecim, 83* 632, 1967

82. Landtman, B & Wallgren, E. L. Infant mortality due to co genital malformations. *Ann Paediat Fenn, 12*·47 1966.
83 Landtman, B., Valanne, E. H. & Aukee, M., Emotional implications of heart disease. A study of 256 children with real and with "imaginary" heart disease. *Ann Paediat Fenn, 14* 71 1968.
84 Lee, W H. Jr., Trezan, D & Pate, J W., Congenital heart disease in infants and neonates. An analysis of mortality in unoperated cases. *J S Carolina Med Ass 60* 70, 1964
85 Lees, M H., Heart failure in the newborn infant. Recognition and management. *J Pediat 75* 139 1969
86. Lees, M H., Cyanosis f the newborn infant. Recognition and clinical evaluation. *J Pediat 77* 484 1970
87 Levy A. M., Hanson, J S. & Tabakin, B S., Congestive heart failure in the newborn infant in the absence of primary cardiac disease. *Amer J Cardiol, 26*·409 1970.
88. Liebman, J & N das, A. S., Heart disease in the newborn. *Pediat Cli N Amer 5* 1087 1958
89 Liebman, J Collum, L. & Belloc, N B., Natural history of transposition of the great arteries. Anatomy and birth and death characteristics. *Circulation, XL*.237 1969
90. Lindesmith, G G., Gallaher M E., Durnin, R. E. Meyer B. W & Jones, J C., Cardiac surgery in the first month of life. *Ann Thorac Surg 2* 250, 1966.
91 Liu, M. C. & Corlett, K., A study f congenital heart defects in mongolism. *Arch Dis Child 34* 410, 1959
92. Louhimo L. Heart surgery in infancy P per presented t the meeting of the Scand Ass Paediat Surg in Turku, June 1970.
93 Malm, J R. & Blumenthal, S., Observations on coarctation of the aorta in infants. *Arch Surg 86* 96, 1963
94 M Donald, A. D., Congenital defects associated with prematurity *Arch Dis Child, 37* 277, 1962.
95 MacMahon, B Association f congenital malformations of the heart with birth rank and ma ternal ge. *Brit J Soc Med, 6* 178, 1952.
96. Mac Mahon, B., McKeown, T & Record, R. G The incidence and lif expectation of children with co genital heart disease. *Brit Heart J 15* 121 1953
97 M hrizi, A. & Drash, A., Birth weight in infants with cyanotic and acyanotic malformations of the heart. *J Pediat, 59* 715, 1961
98. Mehrizi, A. & Drash, A., Growth disturbance in congenital heart disease. *J Pediat 61*·418, 1962.
99 Mehrizi, A., Hirsch, M S. & T ussig, H. B., Congenital heart disease in the newborn period. Autopsy study of 170 cases. *J Pediat 65* 721 1964
100. Mellins, R. B. & Blumenthal, S., Cardiovascular anomalies and esophageal atresia. *Amer J Dis Child, 107* 160 1964
101 Menashe, V D Osterud H. T & Griswold, H E. Mortality from congenital heart disease in Oregon. *Pediatrics, 40* 334 1967
102. Mitchell, S C The ductus arteriosus in the neonatal period. *J Pediat, 51* 1., 1957
103 Naeye, R. L. Unsuspected rgan abnormalities associated with congenital heart disease. *Amer J Path 47*·905 1965
104 Nakamura, F F Hauck A. J & N das, A. S. Atrial septal defect in infants. *Pediatrics 34* 101 1964
105 Neel, J V., Study of major congenital defects in Japanese infants. *Amer J Hum Genet, 10* 398, 1958.
106. Newman, H., Moithan M E. & Osborn, W P Urinary tract anomalies in children with congenital heart disease. *Amer J Roentgen, 106*·52, 1969
107 Noonan, J A. & Nadas, A. S., The hypoplastic left heart syndrome. An analysis of 101 cases. *Pediat Clin N Amer 5* 1029 1958.
108. Okada, R., Johnson, D & Lev M Extracardial malformations associated with congenital heart disease. *Arch Path, 85* 649 1968
109 Olin, C., Rudhe U & Wallgren, G Ventricular septal defect: A study of its natural course in infancy and childhood. *Cardiologia (Basel), 53* 280 1968
110. Ongley P A., Pediatric cardiology in Thailand. *Circulation, 34* 1 1966.
111 Paul, M H., Transposition of the great arteries. In A. J Moss & F H. Adams (eds)· *Heart disease in infants, children, and adolescents*. Williams & Wilkins, Baltimore 1968, p. 527
112. Pernot, C., Stehlin, H Worms, A. M & Bretagne de Kersauson, M C., L atelectasie pulmonaire massive u cours des cardiopathies congenitales du nourisson. *J Radiol Electr 50* 170, 1969
113 Polani, P E. & Campbell, M An aetiological study of congenital heart disease. *Ann Hum Genet 19*.209 1955
114 Powell, E. D U Mongolism and congenital heart disease. *Irish J Med Sci, 397*·40, 1959
115. Rapola, J & Landtman, B., Congenital heart malformations in an autopsy material. *Acta Paediat Scand* suppl 206, 42, 1970.
116. Rausen, A. R., Masako, S & Strauss, L., Twin transfusion syndrome. A review of 19 cases studied at one institution. *J Pediat 66*·613 1965
117 Renwick, D H G., Miller J R. & Paterson, D Estimates of incidence and prevalence of mongolism and congenital heart disease in British Columbia. *Canad Med Ass J 91* 365 1964
118 Richards, M R., Merritt, K K., Samuels, M. H. & Langmann A. G., Congenital malformations of the cardiovascular system in a series of 6.053 infa ts. *Pediatrics, 15* 12, 1955
119 Rothmaler G & Perschel, H. G., Kongenitale Kardiopathie mit Polysplenie. *Paediat Grenzgeb, 7* 317 1968
120. Rowe, R. D Cardiac catheterization in the newborn infant. *Heart Bull (Texas), 9*·61 1960.
121 Rowe, R. D Cardiac malf rmations in mongolism. *Amer Heart J 64* 567 1962.
122. Rowe, R. D & M hrizi, A., *The neonate with congenital heart disease* Saunders, Philadelphia-London-Toronto 1968
123 Rowe, R. D & Uchida, I. A., Cardia malformation in mongolism. A prospective study of 184 mongoloid children. *Amer J Med, 31* 726, 1961
124 Sabiston, D C., Pelargonio, S. & T ussig, H. B., Myocardial infarction in infancy The surgical management f complication f congenital origin of the left coronary artery from the pulmonary artery *J Thor Cardio Surg 40* 321 1960.
125 Schiebler G L., van Mierop, L. H. S. & Krovetz, L. J Diseases of the tricuspid valve. In A. J Moss & F H. Adams (eds.): *Heart disease in infants children, and adolescents* Williams & Wilkins, Baltimore 1968, p 492.
126. Schwartz, E. D Dorst, J P Kuhn J P Rowe, R. D & Varghese, P J Reliability of roentgenographic evaluation of ventricular septal defects in

children. *Johns Hopkins Med J 127* 164 1970.
127 Sham, M. K. M. Congenital heart disease in Taiwan, Republic of China. *Circulation, 39* 251 1969
128. Sherman, F E. *A tlas f congenital heart disease* Lea & Feabiger Philadelphia 1963 pp 123 and 231
129 Storstein, O Rokseth, R. & Sörland, S.: Congenital heart disease in a clinical material. An analysis of 1.000 consecutive cases. *Acta Med Scand, 176* 195 1964
130. T kkunen, R. L. Anthropometric studies in Flemish children. *Ann Paediat Fenn, 8* suppl. 19 1962.
131 Taussig, H. B *Congenital malformations of the heart* Harward University Press, Cambridge 1960.
132. Taussig, H. B., Grawford, H., Pelargonio, S. & Zacharioudakis, S.. Ten to thirteen year follow-up on patients after a Blalock Taussig operation. *Circulation 25*·630 1962.
133 Tyler H R. & Clark, D B.. Incidence f neurological complications in congenital heart disease. *Arch Neurol Psychiat 77* 17 1957
134 Uchida, L. Familial occurrence of congenital heart disease. In J D Keith, R. D Rowe & P Vlad (eds.): *Heart disease in infancy and childhood* The MacMillan Co New York London 1966, p. 159
135. van der Hauwaert, L.. Hartgeruisen in de neonatale periode. *T Geneesk, 23*·697 1967
136. Varghese, P J Calermajer J Izukawa, T., Haller, J A. & Rowe, R. D Cardiac catheterization in the newborn. Experience with 100 cases. *Pediatrics, 44* 24 1969
137 Venables, A. W & Hiller H. G Complications of cardiac investigations. *Brit Heart J 25* 334, 1963
138. Vince D J & Vanandel, M Ventricular septal defect and congenital malformations of the urinary tract. Clinical indications for intravenous urography *Cl Pediat (Phila), 6* 16, 1967
139 Wada J Congenital heart disease. *Jap Circ J 27* 251 1963
140. Walooppillai, N J & J yasinghe, M de S.: Congenital heart disease in Ceylon. *Brit Heart J 32* 304, 1970.
141 Ward, O C. & Docarse, C. Association of extracardiac anomalies with congenital heart disease. *Irish J Med Sci, 7* 423 1968.
142. W terston, D J & Aberdeen, E. Preductal coarctation. In D E. Cassels (ed.): *The heart and circulation in the newborn and infant* Grune & Stratton, New York 1966, p 403.
143 Watson, D G & Rowe, R. D Aortic valve tresia. Report of 43 cases. *JAMA 179* 14 1962.
144 Wiland, O K.. Extracardiac anomalies in association with congenital heart disease. Analysis of 200 necropsy cases. *Lab Invest, 5* 380, 1956.
145. Wilson, M G & Lubscher, R.. Prognosis for hildren with congenital anomalies of the heart and central vessels. *J Pediat 21* 23 1942.
146. Wood, J B., Serugama, J & Lewis, M. G.: Congenital heart disease t necropsy in Uganda. A 16-years survey at Mulago Hospital, Kampala. *Brit Heart J 31* 76, 1969
147 Zechoch, H.. Zur Statistik angeborener Herz und Gefässmissbildungen. *Zbl Allg Path, 100*·426, 1960.
148 *T tralogy of Fallot. A study of all cases diagnosed in Denmark from 1947 till 1965* L H. Rygg (ed.): *Ugeskr Laeg* suppl. 2, 1971 p 17

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge)

150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics, Lisbon, 1962.* Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. *Traumatology, Therapy and Prognosis.* Sw. kr 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic study. Sw kr 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr. 25.— 1964
157. Brante, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm, 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Fabianus, T and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr 20.— 1965
162. Lundmark, *Karl Martin, Bone Marrow Cell Proliferation in* Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw kr 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw kr 35.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W. Focal Spike Discharges in Children, a Longitudinal Study. Sw. kr 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margot, Studies on Encopresis. Sw. kr 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr 30.— 1966
172. *Festschrift in Memory of Constantin Chrysanthopoulos.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the *First Week of Life.* Sw kr 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr 25.— 1967
175. Hänninen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen, 1967 Sw kr 35.— 1967
178. Sjögren, Ivar, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr 20.— 1966
181. Koch, Gösta, Lung Function and Acid Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Ebbe, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1969
188. Meeuwisse, Gunnar W. and Mellin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Kerttula, Antti, *Cardiovascular Responses of the Neonatal Lamb* to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Disease in Children. Sw. kr. 30.—1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kumento, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thom, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969
197. Bentin, Elva, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw kr. 30.— 1969
200. Kanjer, Dina M., Cordeiro, Joaquim, Ramalho, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw kr 35.— 1970
201. Sutherland, Lynette E., Hartnett, Phyllis, Bolle, John U., Bailey, John D. and Lynch, *Matthew J., Bartter's Syndrome. A Report* of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw kr 30.— 1970
202. Fomon, Samuel J., Filer Jr, L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kristian, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. *Effects of Physical Training and Improved Nutrition.* Sw. kr. 85.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Eleventh Scandinavian Paediatric Congress.* Turku, August 3–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr 25.— 1970
209. Rune, Volkmar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw kr. 35.— 1970
210. Rosberg, Georg, Parental Attitudes to Pediatric Hospital Admissions. Sw kr. 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Hakulinen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr 35.— 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. *A Review of 777 Cases.* Sw kr 25.— 1971

Price Swed. kr 25 —

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 214 1971

AN EPIDEMIOLOGICAL STUDY OF CHILD HEALTH AND NUTRITION IN A NORTHERN SWEDISH COUNTY

I. FOOD CONSUMPTION SURVEY

BY GÖSTA SAMUELSON

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 214 1971

From the Department of Paediatrics, University Hospital, Umeå, Sweden

An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County

I FOOD CONSUMPTION SURVEY

by

Gösta Samuelson

UMEÅ 1971

Translated by

BARBARA STEELE

Centraltryckeriet

UMEÅ 1971

CONTENTS

Description of the county of Västerbotten 5

Material 8

Socio-economic conditions 9

Investigative plan of the field studies 12

Methods 1_
The 24-hour recall, 13 The food habit history 15

Statistical methods 16

Results 17
The 4-year-old group, 17 *Nutrient intakes 17 Distribution of nutrient intakes 19 Composition of breakfast, 20 General food habits 20*
The 8-year-old group, 21. *Nutrient intakes 21 Distribution of nutrient intakes, 22. Composition of breakfast, 25 School lunches 25 General food habits 25*
The 13 year-old group, 28. *Nutrient intakes 28 Distribution of nutrient intakes 29 Composition of breakfast, 32 School lunches 32. General food habits, 32.*

Median intakes of energy protein and fat per kg body weight 33

Mean nutrient intakes in relation to energy consumption 33

Comparison between the sexes and between the areas in median energy and nutrient intake 34

Cross-checking between the recall and the food habit history 36

Discussion 37

Summary 42

Acknowledgements 43

References 43

In recent years, the importance of child nutrition, both for children's present health and for their future development, has been increasingly emphasized. However, to date there have been few investigations of the nutrient content of the diets of Swedish infants and children and of their food habits (21, 22, 26, 27, 29, 32, 42, 43). The question also arises whether, and if so, how socio-economic conditions affect children's diet and food habits. Västerbotten county, the county in the northern part of Sweden in which the present study was conducted, includes areas and population groups in which regional traditions persist and those in which urbanization has led to increasing heterogeneity and to changes in the way of living.

The aim of the present study was to determine the nutritive value of the diets of children in different areas of Västerbotten county and to get a comprehensive picture of the children's dietary habits. The study was carried out largely within the same region as that investigated by Odin in 1929-31 (29).

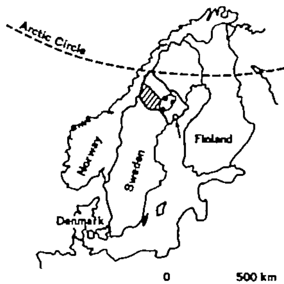


Fig 1. A map of Scandinavia showing the county of Västerbotten and the areas studied. The arrow indicates the city of Umeå; stippling shows the inland area, shading, the mountain foreland.

DESCRIPTION OF THE COUNTY OF VÄSTERBOTTEN

Geographical description

The county is situated in the northern part of Sweden between latitudes 64 and 65 degrees. It is bounded in the east by the Gulf of Bothnia and in the west by the mountains along the Swedish-Norwegian border. Its total area is nearly 60 000 square kilometres, one-eighth of the total area of Sweden. On the map (Fig. 1) the county of Västerbotten is outlined. The marked areas indicate the regions in which the investigation was conducted. The easternmost part of the landscape consists of a lowland coastal region about 50 km wide. A number of river valleys cut across the countryside. Since early times the valleys have provided favourable natural conditions for human settlement, and even at present the centres of population are concentrated along them. At the mouths of the two largest rivers lie the city of Umeå and the city of Skellefteå. From this region, children from the *city of Umeå* were selected. The city of Skellefteå was not included in the study.

West of the lowland region is the *inland area*, 100–200 km wide, which consists mainly of forest and arable land broken up by river valleys. The region also contains extensive swamps. Most of the inland area lies 200—300 metres above sea level. Settlements are concentrated to the larger valleys. The town of Lycksele, the commercial centre of the inland area, was not included in the investigation. The inland area is represented in the investigation by two communes in central Västerbotten, namely the rural communes of Lycksele and Åsele with a total area of 8[illegible]75 square kilometres.

Fig 2 A schematic map of the county of Västerbotten showing geographical differences height above sea level and population density in the main centres. 1=city of Umeå, 2=inland area, 3=mountain foreland. The broken lines (— — —) show the boundaries of the investigated parts of the inland area and the mountain foreland.

West of this forest belt, the landscape undergoes a gradual transformation in *the mountain foreland* Its eastern part resembles the inland area, but its altitude increases with distance from the coast. The eastern part consists of forest and arable land 300—500 metres above sea level. Although part of the population *in this region is concentrated* in villages, it is mostly scattered over a vast area. Farthest west towards the Norwegian border lies the true mountain region 80—100 km wide. The mountains reach a maximum height of about 1700 metres above sea level. The two communes in this region that were *included in this investigation*, namely the communes of Dorotea and Vilhelmina, cover an area of 10 92. square kilometres These communes border in the east on the communes of Lycksele and Åsele, in the west on Norway The two main villages bearing the same names as the communes were included in the study

The mountain foreland thus differs from the inland area, partly in that the region as a whole is at a higher altitude and partly in that it includes a mountainous region.

A more detailed map of the county Fig. -- *schematically illustrates the geographical* differences within the county and the principal villages and towns.

Population and economy
On January 1 1968 the entire county had 235 230 inhabitants.

City of Umeå Within the administrative area of the city there were 51 952 inhabitants. The county administration is concentrated in Umeå, which is also a commercial and educa

tional center In 1965 after a ten year period of development, the University of Umeå was officially dedicated. The city's economic life depends on the educational institutions, the county administration, military establishments and the medical centre, and to a lesser degree, on industry Industrial production is mainly based on forest products such as wood pulp and lumber

Inland area A large part of the population of this middle region of the county lives in sparsely-populated rural areas. In the part of the inland area included in the investigation there are few larger population centres. The community of Åsele, with about *2400* inhabitants, is one of the main centres.

The economy is dominated by forestry often combined with small farming There is some mining industry Otherwise the area is the least industrially developed in the county Unemployment has been a major problem and has led to migration from the region during the 1960's.

Mountain foreland The population in this area is also scattered in sparsely populated rural areas The two communes included in the investigation, Dorotea and Vilhelmina, together had about 13 900 inhabitants on January 1 1968 The central villages of Dorotea and Vilhelmina had about 1500 and 3000 inhabitants respectively The economy is based on forestry often combined with small farming. In the villages, commerce and small wood industries are important sources of employment. Tourism is also an important source of income

Climate

The climate is characterized by long, cold winters and short intense summers. In the coastal region the ground is covered with snow about five months of the year and in the two rural areas about 1—2 months longer ( ) The mean temperatures during the year in the different areas are shown in Table 1

Communications

The county has a relatively well-developed network of roads which are easily passable even in the winter In spite of the vast areas, 97 per cent of the population live within a two hour's car journey from the nearest hospital *(44)*

The railway network is chiefly important for freight transport. During the past decade, airports have been built near Umeå, Skellefteå and Lycksele.

The county has two major harbours. One is the outer harbour of the city of Umeå, which is open 11 months of the year on an average. The main exports are wood pulp board, paper and other wood products.

Genetic heterogeneity of the population

The population of Västerbotten county is genetically heterogeneous due to the fact that three different population elements (Lapps, Finns and people of South Swedish origin) are mixed in the county (7) Significant regional heterogeneity has been found in the *ABO Rh* and *P* blood group systems. Lappish influence is found mainly in the north-western parts of Västerbotten Hence the three areas studied in this investigation should have only a minor Lappish population element.

The two communes of the inland area are heterogeneous with respect to their ABO-gene frequencies. In the mountain foreland, the communes of Dorotea and Vilhelmina are *similar in these respects and similar* to the commune of Åsele (7)

The population of the city of Umeå is also heterogeneous, since a large percentage have moved there from other parts of Sweden.

Table 1 *Mean temperatures in C° in Sweden at latitude 64 degrees at sea level and at 500 metres (Ångström 1958)*

	Ja uary	April	J ly	October
Sea level	8.2	+1.3	+16.3	+2.7
500 metres	–10.0	1 3	+13.3	+0.4

Table 2. *Age sex and geographical distribution of the 1401 children studied*

Age group	4 years			8 years			13 years		
Median age	4 years 5 months			8 years 4 months			13 years 4 months		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
City of Umeå	99	99	198	100	100	200	100	100	200
Inland area	—	—	—	98	90	188	91	111	202
Mountain foreland	—	—	—	99	96	195	114	104	[illegible]
Total	99	99	198	297	286	583	305	315	620

MATERIAL

All the children who took part in the study were selected from the official population register for Västerbotten county The age, sex and geographical distributions of the 1401 children who were actually studied are shown in Table 2. Of the 1488 children who were asked to take part in the investigation 87 (7 per cent) were omitted. The reasons for these omissions are given in Table 3

Age groups

The material from the *city of Umeå* consisted of three groups of children, those who had attained the ages of 4 8 and 13 years during the year of the study 1967 The groups are referred to below as the 4- 8 and 13-year old groups. From the two other regions studied, the *inland area* and the *mountain foreland* only 8 and 13 year-olds were selected.

No 4 year-old group was included from outside the city of Umeå because of the difficulties involved in reaching preschool children for clinical examination. Because of the great distances, a study of these children would have required complex administrative

Table 3 *Distribution of omissions in different areas*
1=City of Umeå, 2=Inland area, 3=Mountain foreland.

	1	2	3	Total	Per cent
Invited	635	411	442	1488	100.0
Moved	29*	1	18	59	4.0
Remained to examine	606	399	424	1429	96.0
Non-Caucasian (genus incertum)	1	—	—	1	0.1
Mental retardation	5	3	6	14	1.0
Blindness (cerebromacular degeneration)	—	—	1	1	0.1
Diabetes mellitus	—	3	1	4	0.3
Chondrodystroph	—	1	—	1	0.1
Remained to examine	600	392	416	1408	94.6
Refused	—	—		2	0.1
Excluded because food consumption recall was incomplete, due to					
Acute gastroenteritis	2	—	1	3	0.2
Upper respiratory infection	—		—	2	0.1
Final material taking part in the investigation	598	390	413	1401	94.2

Fifteen 4-year-old

organization, the study would have been difficult to carry out, and there would probably have been a large number of omissions

In all age groups the children's birth months were uniformly distributed over the year. Mean and median ages have been calculated from the ages in months and days at the time of investigation. The mean age as well as the median age of the children in the 4-year-old group was 4 years, 5 months, in the 8- and 13-year-old groups, 8 years 4 months and 13 years, 4 months respectively.

Number of children

The aim of central selection from the official population register was to choose about 200 children for the study, half boys and half girls, within each age group and from each of the three regions. The total numbers of children in the three age groups in Umeå proper at the time of selection in May 1967 were 398 children born 1963 (4-year-olds), 358 children born 1959 (8-year-olds) and 334 children born 1954 (13-year-olds).

Within the *city of Umeå* the population was registered in districts by block, according to residential address. All the children in the three age groups in Umeå proper were assigned numbers in the order in which they were registered. Each age group formed a population sample with boys in one group, girls in another. By a systematic selection process, every other child was chosen from these groups in all districts. Within each age group 200 children were chosen, half boys and half girls, uniformly distributed throughout the city.

Only districts with entirely urban populations were included in the study. The 4-, 8- and 13-year-olds selected for the investigation represented 25 per cent, 28 per cent and 30 per cent of the total numbers of children in these age groups in the city of Umeå as a whole at that time.

At the time of the primary selection of the material a number of children in excess of the desired number were selected simultaneously and in the same way, forming a reserve group. A pilot study had shown that a drop-out rate of 5—10 per cent was to be expected, due either to children's moving away before the start of the investigation or to the fact that children chosen proved to be chronically ill. From the reserve group 16 four-year-olds, 5 eight-year-olds and 14 thirteen-year-olds were chosen in the same way as the other children to be substitutes for the children who dropped out for the above reasons. In this way the primary material—the number of children in the city of Umeå invited to take part in the study—came to consist of 216 four-year-olds, 205 eight-year-olds and 214 thirteen-year-olds.

In the *inland area* there proved to be about 200 children in each of the 8- and 13-year-old age groups, and thus all children in these age groups were included in the study. The primary material for the inland area consisted of 201 eight-year-olds (101 boys and 100 girls) and 210 thirteen-year-olds (95 boys and 115 girls).

In the third region studied, the *mountain foreland* there were also about 200 children in each of the age groups, and thus all the 8- and 13-year-olds were included. The primary material consisted of 09 eight-year-olds (108 boys and 101 girls) and 233 thirteen-year-olds (1_2 boys and 111 girls).

SOCIO-ECONOMIC CONDITIONS OF THE GROUPS STUDIED

All information about social conditions was obtained in personal interviews with the children's mothers in connection with the dietary interviews. The percentage distribution of the collected data in different age groups and areas is given below.

Number of children in the family

The families in the two rural areas were significantly larger than families in the city of Umeå (Table 4)

Table 4 *Percentage distribution of the number of children in the family*

	No.	N of children in the family								
		1	2	3	4	5	6	7	8	≥9
City of Umeå										
4 years	198	14	53	1	7	5				
8 years	200	13	36	31	13	5	1	0	1	
13 years	200	10	33	31	16	7	2	1		
Inland area										
8 years	188	3	36	24	0	11	3		0	1
13 years	202	5	23	31	15	18	4	2	0	2
Mountain foreland										
8 years	195	9	30	24	14	1	5	4	1	1
13 years	218	6	4	[illegible]3	16	17	3	5	1	3

Parents education

The parents educational levels were classified according to number of years of education and type of schooling as follows

1 = elementary school only (≤6 years)

2 = education beyond elementary school up to a total of 9 years formal education
   a) more than 6 but less than 9 years formal education
   b) complementary schooling after some working experience
   c) vocational school

3 = 9—11 years of formal education
   a) began, but did not complete, gymnasium
   b) degree from technical or business school
   c) other education, at least 2 years

4 = 12 or more years of formal education. Degree from gymnasium academic studies etc.

The parents of the investigated children in the city of *Umeå* had a significantly higher avearge educational level than the parents in the two rural areas (Tables 5 and 6).

In the *inland area* 2 per cent of the mothers and 3 per cent of the fathers of both the 8 and 13-year-old groups had had more than 12 years of formal education. 80 per cent of both the mothers and the fathers of both age groups had had only elementary school education.

In the *mountain foreland* the percentages for both age groups were approximately the same as in the inland area. There were no significant differences between the two rural areas with respect to the mothers or fathers education.

Table 5 *Percentage distribution of mother s education*

	N	Years of education			
		≤6	6—9	9—11	≥12
City of Umeå					
4 years	198	34	23	26	17
8 years	200	55	19	17	9
13 years	200	56	16	21	7
Inland area					
8 years	188	77	12	9	2
13 years	202	80	14	4	2
Mountain foreland					
8 years	195	80	11	8	1
13 years	218	83	12	4	1

Table 6. *Percentage distribution of father s education*

	No.	Years of education				
		≤6	6—9	9—11	≥12	unknown
City of Umeå						
4 years	198	41	14	12	29	4
8 years	200	45	23	13	18	1
13 years	200	45	21	11	[illegible]2	1
Inland area						
8 years	188	74	15	5	3	3
13 years	202	81	9	4	3	3
Mountain foreland						
8 years	195	78	12	5	3	2
13 years	218	81	11	3	2	3

Dwelling space

The number of persons per room in the home was calculated, including the kitchen as a room (Table 7). For both the 8 and 13-year old groups, the dwelling space per person was significantly larger in the city of Umeå than in the mountain foreland.

Table 7 *Percentage distribution of dwelling space expressed as persons per room The kitchen was included as a room*

	No.	Persons per room					
		≤0.5	1.0	1.5	2.0	2.5	3.0
City of Umeå							
4 years	198	2	75	20	3	0	0
8 years	200	4	67	26	3	0	0
13 years	200	7	70	19	4	0	0
Inland area							
8 years	188	4	61	29	5	0	1
13 years	202	5	62	25	7	1	0
Mountain foreland							
8 years	195	1	59	30	9	1	0
13 years	218	3	61	28	7	1	0

Family's total income

The data on income refer to the parents combined yearly income, before deduction of income tax and including all types of supplementary economic aid. Table 8 gives the total family income on a per capita basis. The medians for the parents combined income were significantly higher for all age groups in the city of Umeå than in the rural areas. There were no significant differences between the latter two areas with respect to family income.

In addition to the above data, the mothers ages (years of birth) were registered. All these data were included in the analysis of the relationship between general and oral child health, food habits and socio-economic conditions (35).

Housing conveniences

In the city of Umeå, most families had access to running water drainage an indoor toilet and central heating. In the two rural areas, a few per cent lacked running water and drainage and 2—12 per cent lacked an indoor toilet and central heating. In the city of Umeå, 1—3 per cent lacked bath or shower facilities, whereas 7—10 per cent in the inland area and 18—21 per cent in the mountain foreland lacked these conveniences.

An electric stove was the most common type in all areas. In the rural areas, many families also had a wood-burning stove.

Nearly all families in the city of Umeå had a refrigerator In the rural areas, 14—28 per cent lacked a refrigerator

Table 8 *Income per capita in Swedish crowns*[1] *The figures are percentages*

	No.	≤1.000	≤2.000	≤3.000	≤4.000	≤5.000	≤6.000	≤7.000	≤8.000	≤9.000	≤10.000	>10.000
City of Umeå												
4 years	198	0	0	1	3	7	12	14	11	9	8	34
8 years	200	0	0	1	6	8	12	15	14	9	4	31
13 years	200	0	0	0	3	6	10	10	14	10	10	37
Inland area												
8 years	188	1	3	10	12	18	17	13	11	4	3	8
13 years	202	2	4	10	17	14	18	13	6	4	4	8
Mountain foreland												
8 years	195	1	6	13	13	16	12	16	8	5	2	8
13 years	218	4	5	11	19	15	13	11	6	3	6	7

The English pound and the U.S. dollar are worth approximately 12 Sw cr and 5 Sw cr respectively

On the other hand, a freezer of some type was more common in the rural areas than in the city of Umeå. In the rural areas, 87—93 per cent had some type of freezing facilities in the home compared with 61—74 per cent in the city of Umeå.

INVESTIGATIVE PLAN OF THE FIELD STUDIES

Periods of investigation

The dietary interviews were held simultaneously in the three areas during September December 1967 A medical, odontological and haematological examination (34 36 37) of the 4-year-olds was performed during the period November December 1967 for the 8 and 13-year-olds, during the period September December 1967

Performance of the field study

The performance of the dietary interviews is described under methods. The group of investigators for the field studies consisted of a paediatrician (the author) a laboratory technician, a dentist and a dental assistent.

The team began the investigation in the city of Umeå and remained there one week. They then moved to the inland area to investigate children there. After one week, they moved to the mountain foreland, also for one week of investigation. They then returned to Umeå to begin another round.

MFTHODS

The data on diet were collected partly by the use of a *24-hour recall* and partly by direct questioning about food habits in the present study the latter interview is called the *food habit history* (p 15) General procedures concerning the design of the interviews, the recording of food consumption, and the conversion of food consumption data to nutrient data, were adapted from manuals on nutrition surveys (25 31)

Information to the parents

About two weeks before the start of the investigation, the parents of the children to be included in the study were notified by letter that a study of their children's diet was to be conducted during the fall of 1967 In this message to the parents the reason for the study was explained and they were informed that an interviewer would visit their homes. The time for the visit was not stated. Nor were the parents told that a medical and odontological examination would be given during the same period.

The interviewers

The interviews were conducted by five interviewers from the county trained at the National Central Bureau of Statistics (SCB), Stockholm. All had had many years of experience in interviewing techniques and all were familiar with household purchasing and had had experience with children in previous fields of employment. In order to give them special instruction in the taking of a dietary interview they were brought together for two days on two different occasions, separated by a two-month interval at the Department of Paediatrics, Umeå University Hospital On these occasions they were given detailed information about the plan of the investigation. This information was given by the author and the dentist recording the oral data together with a dietitian who had had extensive experience with previous dietary studies in Sweden. The questions on the interview form and their significance were discussed in detail.

At the time of the first meeting, test interviews of the 24-hour recall type were held with hospitalized children. Prior to this training exercise, they were instructed by a dietitian experienced in the recall method. Included in this instruction was a detailed description of how quantitative data should be obtained and recorded.

Assignment of the interviewers

The interviewers were assigned to the different areas two of them were responsible for the dietary interviews in the city of Umeå, one for the 4 year-olds and one for the 8 and 13 year-olds. Two were assigned to the 8 and 13 year-olds in the *inland area* one in the commune of Lycksele and one in Åsele. The *mountain foreland* was divided so that an interviewer based in Vilhelmina conducted all the interviews in the Vilhelmina area. The Dorotea area was divided between the two responsible for the interviews in the *inland area*

The interview situation

The 24 hour recall and the food habit history were carried out in the following way

The 4-year-old group The interviews were held with the mother or in 14 cases, with another person taking care of the child. The children in this age group were not questioned. After introductory questions regarding the general schedule of meals, the 24-hour recall was taken followed by the food habit history 180 interviews were conducted entirely according to instructions, that is, without previous contact with the home. In 20 cases it was necessary for the interviewer to first contact the mother by telephone to find out roughly when she would be at home. An exact time for the interview was never decided upon in advance In the 20 cases mentioned, the mothers had irregular working hours outside the home and it was thus also necessary to visit the person who cared for the child during the day to obtain a complete dietary interview

The 8 year-old group The children were questioned together with the mother Usually the child gave the primary information in the recall and the mother gave supplementary data, for example regarding the manner in which the food was prepared. In certain cases the supplementary information was given by the father or another person. The child and parent were interviewed at home during the afternoon or evening. Only in a few exceptional cases was the interview conducted by telephone. As with the 4-year-olds, the 24 hour recall was taken first, followed by the food habit history

The 13 year-old group The child was first interviewed alone during the school day as to his 24-hour consumption. The child then supplied the food habit history as to how often various foods and dishes were consumed. In the afternoon or evening the information was supplemented by an interview with the mother at home, at which the child was not always present. The child s answers were checked in this way and if there were differences in the information given by the mother and by the child, these were discussed with the child and the mother Usually the child s original information became the definitive data.

The 8- and 13-year-olds were always asked for information regarding the consumption of sweets and fruit and the frequency of eating between meals.

Days for the interviews

The interviews were held on weekdays, Monday through Saturday They were evenly distributed over the days of the week with the exception of Saturday when fewer interviews were held. Saturday is a free day for many in Sweden, and it was difficult to reach people for interviews on this day No interviews were held on Sunday and Saturday s consumption is thus not represented in the study Sunday s consumption, on the other hand, was recorded at interviews held on Monday

The 24-hour recall

The child s total consumption during the previous 24 hours was recorded meal by meal, starting with the meal most recently con-

sumed Finally the child was questioned closely about all between meal consumption. The time of each occasion on which food was consumed was noted. In order to help the child and/or the mother to remember what the child had eaten it was sometimes necessary to use leading questions of the type, 'Did you eat a sandwich? What kind of bread was it? How much butter or margarine? What kind of spread or filling? The aim was to obtain as exact information as possible as to the amounts consumed.

Vegetables note was made of the type size and the number of quarters or slices (tomatoes), leaves (lettuce) spoonfuls (grated carrots)

Fruits and berries type, number number of spoonfuls or similar data was noted and whether *fruit juices* were canned, bottled or packed in paper cartons.

Potatoes and *root vegetables* type, number or number of spoonfuls was obtained.

Milk and cheese the type, brand and amount of milk consumed was recorded in decilitres or as the number of glasses or cartons of known volume, and the amount of cheese as number of slices. The thickness of the slices was noted. The percentage fat in milk and cheese was also recorded if possible. In several cases the interview was later supplemented on this point by interviewing the mother or the personnel in the school cafeteria, who could almost always supply this information.

Meat and fish cuts and types were recorded. It was noted whether meat contained bone, also whether it was served as whole meat or was mixed with other ingredients in a patty or meat loaf The term portion was avoided as far as possible When this was not possible, the interview was later supplemented by information from the mother or the cafeteria personnel. The amount the child usually ate, number of slices, approximate size thickness etc., was substituted for statements regarding portions. The type of sausage such as pork beef frankfurter etc. was noted as well as the brand and price, if possible. The number and size of sausage or sausage slices was also noted.

Eggs number quarters or slices were recorded

Bread and cereal products the type was recorded, eg rye cake, soft loaf French bread, tea cakes etc. Crispbread, usually of commercial manufacture, was recorded as number of pieces, and for the thin bread made from barley wheat or rye flour that is commonly eaten in the northern part of Sweden, measurements were given. Dishes such as spaghetti and macaroni were recorded in measures such as a coffee cup or a half or a quarter of a plateful. For zwieback, biscuits, buns, cakes and baked goods, the number of pieces, their size, and, if possible, the brand name were noted. Gruel and porridge were recorded by type, and amounts were expressed in terms of a bowl of known volume.

Butter and margarine these items were noted mainly as spread on sandwiches and the amount used was expressed as large, average or small corresponding to 10 7 or 5 grams of butter or margarine respectively These amounts are those given by the Swedish consumers institute (Konsument Institutet) and are based on experience.

Sugar The amount consumed was expressed in teaspoonfuls or lumps. It was noted whether sugar had been added to juice at the time of drinking. With respect to confectionery products such as candies or ice cream, the number of units, the type or brand and the price were noted.

Information as to the method by which food had been prepared was obtained from the mother or from the personnel in the school cafeteria, e.g whether it had been fried, grilled, boiled or baked It was noted whether butter or margarine had been used in preparation.

The recall method was tested on 8 and 13-year-olds at school lunches in the city of Umeå, using the double-portion technique (33)

Transforming and coding of recall data

All the collected data on consumption during a 24 hour period were converted into terms of nutrient content in cooperation with the Nutrition Division of the Swedish National Institute of Public Health. A computer system developed by the Institute in cooperation with IBM in Sweden (45) was used in processing the dietary data The nutrient content of the diets was calculated using both food composition tables (1) and all available pertinent information from such sources as the consumers institute (Konsument Institutet), the food industry and the results of continuous nutrient analyses performed by the Swedish National Institute of Public Health.

In the food composition tables used, the energy content of foods is calculated using the following factors Fat 9.3 kcal/g (39 kJ/g), protein and carbohydrate: 4 1 kcal/g (17 kJ/g) For protein, the nitrogen factor 6.25 is used for mixed foods in the calculations. Carbohydrate content per 100 g is calculated as the difference 100 (water + fat + protein + ash)

Vitamin A is in the present study given in mg retinol equivalents from preformed vitamin and β-carotene according to FAO/WHO (16)

Niacin equivalents include dietary sources of the vitamin itself plus 1 mg equivalent for each 60 mg of dietary tryptophan.

The nutritional value and energy content of the food products consumed and the standard recipes for various dishes were kept in an electronic computer system in a punched card master file. After coding the recall data according to the nutrient code and actual amount, the data were transferred to magnetic tape for processing.

The food habit history

A questionnaire, in the present study called the food habit history was constructed The purpose of taking this history was twofold

1 to obtain information about the general food habits of the investigated children,
2. to record the kinds of foods and dishes that were included in the children s daily food consumption. In this way it was possible to obtain a rough check on the individual children s recalls of their consumption during a 24-hour period.

Questions were asked about the children s frequency of consumption of a number of foods and dishes. Tables 16 *a* and 16 *b* list the foods, beverages and dishes that were included. A special group of questions concerned between-meal consumption. In Table 17 the foods and beverages which were asked about as consumption between meals are listed. The four groups consisted of the following foods. *Fruit* mainly apples, oranges, bananas *Sweets* chocolate, pastilles, raisins, candies, chewing gum etc. *Buns and cakes* all types of sweet buns and cookies. *Soft drinks* juice, refreshing drinks such as Coca Cola etc. The frequency of consumption was graded according to the following never once every other month twice a month one a week several (four) times a week once a day 2—3 times a day and 4 or more times a day' This frequency scale was prepared in advance. In the interview situation, the mothers or for the 13 year-olds, the children themselves, were handed a form giving the frequency alternatives. The interviewer then posed the questions concerning the frequency of consumption of different foods.

In addition to the food consumption frequencies, the general pattern of meals during the day was ascertained. Foods liked and disliked were noted. Questions were asked about the number of sandwiches consumed and the kind of sandwich filling usually used.

STATISTICAL METHODS

The quantitative variables investigated are characterized by measures of location, dispersion and correlation (40)

Measures of location.

a) The mean value, defined as

$$M = \bar{X} = \frac{1}{n}\sum_{i=1} X_i$$

where n is the number of cases and x_i is the values of variable x for case number i ($i = 1,2, \quad n$)

b) The median value, defined as the value below which 50 per cent of the population lies.

c) The upper and lower quartiles, defined as the values below which 75 per cent and 25 per cent of the population lie.

Measures of dispersion

In connection with the mean value, the standard deviation was used defined as

$$S D = \sqrt{\frac{1}{n \quad 1}\sum_{i=1} (X_i \quad \bar{X})^2}$$

and the standard error of the mean, defined as

$$S.E.M. = \frac{S D}{\sqrt{n}}$$

Measure of correlation

As a measure of correlation between two variables, X and Y Person s correlation coefficient, defined as

$$r_{XY} = \frac{\sum_{i=1} (X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1} (X_i - \bar{X})^2 \sum_{i=1} (Y_i - \bar{Y})^2}}$$

was used.

Significance tests

1 For testing whether a variable was identically distributed in different populations, the Chi-square test was used.

2 For testing the differences between means, the following approximately normally distributed ratio was used

$$z = \frac{\bar{X} - \bar{Y}}{\sqrt{S.E.\bar{X}^2 + S.E.\bar{Y}^2}}$$

3 For testing the differences between medians, the median test was performed (9)

4 For testing whether a true correlation coefficient differed from 0 the following ratio was formed

$$t = \frac{r_{XY}\sqrt{n-2}}{\sqrt{1 - r_{XY}^2}}$$

which, if the true coefficient equals 0 follows a Student s t-distribution with n-2 degrees of freedom.

Significance levels

The decision whether or not to reject the null-hypothesis is based upon the observed value of the test variable formed for the specific situation, its distribution being known when the null hypothesis holds Let p be the probability of getting a value of the test variable at least as great as the observed, assuming the null-hypothesis to be true.

The deviation from the null-hypothesis is said to be non-significant if

$0\ 05 < p$

$0\ 01 < p$ (*)

$1 < p$ (**)

$p < 0$ (***)

RESULTS

For each age group the results are presented as follows

A) Relation to the recommendations by the Food and Nutrition Board of the National Academy of Sciences, National Research Council in the USA, Recommended Dietary Allowances, 1968 (19) and for fat by the Swedish National Institute of Public Health (41)
B) Distribution of nutrient intakes according to meals and the contributions of different food groups.
C) Composition of breakfast.
D) School lunches.
E) General food habits.

For all nutrients, possible losses in cooking were not taken into account when calculating the nutrient content in the diet.

As shown in Figs. 4 8 and 12, the daily food intake for all age groups was distributed among breakfast, lunch, dinner an afternoon snack, and evening meal before bedtime and irregular between-meal eating.

I 4-YEAR-OLD GROUP

The mean and median values for the energy and nutrient content of the diet according to the 24-hour recall, are given in Tables 9 *a* and 9 *b* Since the boys had a higher energy intake than the girls, their total intake of nutrients was greater (Table 22)

A. *Actual nutrient intakes in relation to recommended dietary allowances*

The mean intakes of energy protein and calcium were above the recommended levels, as were the intakes of vitamin A, thiamine, riboflavin, niacin-equivalents and vitamin C (Fig. 3) The average intake of fat in the diet was above the level of 25—35 per cent of the

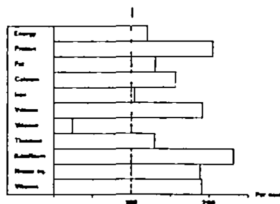


Fig 3 4-year-old group Mean energy and nutrient intakes per cent of the Recommended Dietary Allowances of the Food and Nutrition Board, USA, 1968. The mean intake of f is given in per cent of the mean recommendation (30 per cent of the energy intake) proposed by the Swedish National Institute of Public Health The arrow indicates the recommended level.

Table 9a. *The 4-year-old group Mean values and standard errors of the means of energy and some nutrients in food consumed accord ng to 24-hour recall Figures in italics are standard errors of the means.*

Sex No.	Energy[1] kcal	MJ	Protein g	Fat g	Carbohydrate g	Calcium mg	Iron mg	Vitamin A Retinol eq mg	β-carotene mg	Vit. D μg	Thiamine mg	Riboflavin mg	Niacin eq. mg	Vit. C mg
Boys	1915	8 0	67	83	207	1346	11 1	1.0	1.5	2 6	1 1	2.2	20.4	81
99	*58*	*0.2*	*2.0*	*4.0*	*6.0*	*48*	*0.4*	—	—	*0.2*	*0.05*	*0.07*	—	*6.0*
Girls	1642	6.9	55	71	185	1142	9.8	1.0	1.0	2 2	0.9	2.0	17 1	72
99	*47*	*0.2*	*1.6*	*2.8*	*5.7*	*38*	*0.4*	—	—	*0.2*	*0.04*	*0.08*	—	*5.0*
Total	1779	7 4	61	78	196	1244	10 5	1 0	1 3	2.4	1.0	2.1	19.0	76
198	*37*	*0.2*	*1.3*	*2.3*	*4.1*	*31*	*0.3*	—	—	*0.1*	*0.03*	*0.05*	—	*3.9*

1 kcal = 4 184 kJ (kiloJoule); 1 MJ (megaJoule) = 1000 kJ.
In the calculations, the dispersions of vitamin A, β-carotene and niacin eq. are not given because of difficulties in obtaining reliable data.

only 0 4—1.7 mg by the other meals. One-third of the iron intake came from meat, fish and eggs, and almost as much came from cereal products and bread (Table 10) which in Sweden is mostly baked from iron-enriched flour (5 mg iron/100 g flour since 1971 6.5 mg/100 g flour)

Vitamin A thiamine riboflavin and niacin Vitamin A and niacin came largely from the group meat, fish and eggs. 31 per cent of the thiamine and 72 per cent of the riboflavin was supplied by milk and milk products (Table 10) About 20 per cent of the vitamin A was derived from β-carotene.

Vitamin C 47 per cent of the vitamin C was obtained from fruit and berries (Table 10)

Vitamin D Most of the vitamin D in the diet came from vitamin-enriched margarine and butter and from the group meat, fish and eggs (Table 10)

C. *Composition of breakfast*

According to recall, the most common breakfast consisted of milk or chocolate milk and sandwiches or sweet buns 5 per cent of the children ate no breakfast (Table 11)

Table 11 *The composition of breakfast for 198 four year-olds The figures are percentages*

Type of breakfast	/
H prepared breakfast	0
Gruel or gruel nd sandw ches	10
Porridg and milk, or porridge, milk nd sandwiches	9
Cultured milk, prepared cereal or sandwiches	11
Milk, prepared cereal and sandwiches or sweet buns	18
Choc lat milk and sandwiches or sweet buns	26
Milk or chocolate milk	3
Tea and sa dwiches and/or sweet b ns	10
Sandwiches	1
Soft drinks nd sandwiches and/ sweet buns	6
Coffee and sandwiches	0
O her such as sof dri ks or fruit	1
No breakfast	5

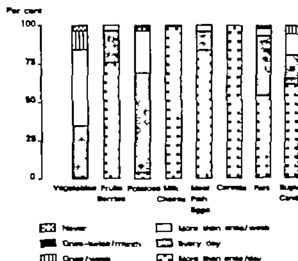


Fig 5 4-year-old group Frequency f consumption of different foods classified according to food groups.

E. *General food habits*

The general pattern of consumption of different foods and dishes obtained through the food habit history is summarized in Fig 5 All foods and dishes have been classified according to food groups It appears from the figure that 35 per cent of the children ate vegetables daily 96 per cent berries or fruit daily 70 per cent potatoes and 96 per cent meat, fish or eggs daily All the children ate bread and butter or margarine and drank milk daily 80 per cent of the children consumed sugar and candy daily There were no significant differences between the sexes with respect to the frequency of consumption.

Foods liked Pancakes, sausage, spaghetti fish and macaroni were the five foods most liked.

Foods disliked Brown beans, pea soup soup meat and fish were the five foods least liked.

Sandwich consumption On an average, the children consumed 2—3 sandwiches per day For 80 per cent, the most common sandwich filling was cheese 9 per cent usually ate plain sandwiches without filling.

II 8 YEAR-OLD GROUP

The means and medians for the energy and nutritional content of the diet, according to the 24-hour recall is given in Tables 12 *a* and 12 *b*. The total intake of energy and nutrients was greater for boys than for girls in all three areas, and greater in the rural areas than in the city of Umeå. For significances of the differences, see Tables 22 and 23.

A. *Actual nutrient intakes in relation to recommended dietary allowances*

Figures 6 and 7 show the similarity of the composition of the diet in the three areas.

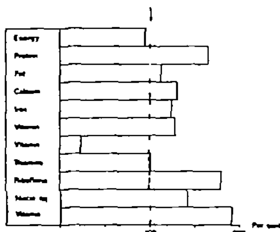


Fig. 6. 8-year-old group in the city of Umeå. Mean energy and nutrient intakes in per cent of the Recommended Dietary Allowances of the Food and Nutrition Board, USA, 1968. For f t, see Fig. 7

Table 12a. *The 8 year-old group. Mean values and standard errors of the means of energy and some nutrients in food consumed according to 24-hour recall. Figures in italics are standard errors of the means*

Sex N	Energy[1] kcal	Energy[1] MJ	Protein g	Fat g	Carbohydrate g	Calcium mg	Iron mg	Vitamin A Retinol eq. mg	Vitamin A β-carotene mg	Vit. D g	Thiamine mg	Riboflavin mg	Niacin eq.[2] mg	Vit. C mg
Boys	2349	9.8	77	107	255	1464	14.5	1.2	1.6	3.4	1.3	2.5	23.5	78
297	*38*	*0.2*	*1.3*	*2.2*	*4.6*	*29*	*0.4*	—	—	*0.2*	*0.03*	*0.05*	—	*3.1*
Girls	20_7	8.5	6	92	19	13_4	12.0	1.0	1.5	3.3	1.2	2.2	20.0	68
286	*33*	*0.1*	*1.2*	*2.0*	*3.7*	*26*	*0.4*	—	—	*0.4*	*0.0*	*0.04*	—	*_5*
Total	2188	9.2	72	99	237	1384	13.3	1.1	1.6	3.4	1.3	2.4	21.9	73
583	*25*	*0.1*	*0.9*	*1.5*	*3.0*	*20*	*0.3*	—	—	*0.2*	*0.02*	*0._3*	—	*2.0*

1 kcal = 4.184 kJ (kiloJoule) 1 MJ (megaJoule) = 1000 kJ
See note, Table 9a.

Table 12b. *The 8 year-old group. Median values, upper and lower quartiles of energy and some nutrients in food consumed according to 24-hour recall*

Sex N	Percentiles	Energy kcal	Energy MJ	Protein g	Fat g	Carbohydrate g	Calcium mg	Iron mg	Vit. A Retinol eq mg	Vit. D μg	Thiamine mg	Riboflavin mg	Niacin eq mg	Vit. C mg
Boys	25th	1925	8.1	61	78	201	1092	10.4	0.6	1.8	1.0	1.8	17.4	42
297	50th	2289	9.6	75	104	242	1450	13.3	0.9	2.7	1.2	2.4	21.8	63
	75th	2668	11.2	90	127	293	1775	16.2	1.1	4.0	1.5	2.9	28.1	97
Girls	25th	1602	6.7	51	68	170	989	8.4	0.6	1.5	0.9	1.7	14.5	39
286	50th	1966	8.2	65	87	211	1270	10.7	0.7	2.2	1.1	2.1	18.8	58
	75th	2344	9.8	79	112	259	1594	13.9	0.9	3.1	1.4	2.6	24.1	87
Total	25th	1739	7.3	56	72	183	1040	9.2	0.6	1.6	0.9	1.8	15.7	40
583	50th	2138	9.0	69	96	228	1351	11.9	0.8	2.3	1.2	2.3	20.2	60
	75th	2555	10.7	86	121	275	1673	15.0	1.0	3.6	1.5	2.8	26.5	92

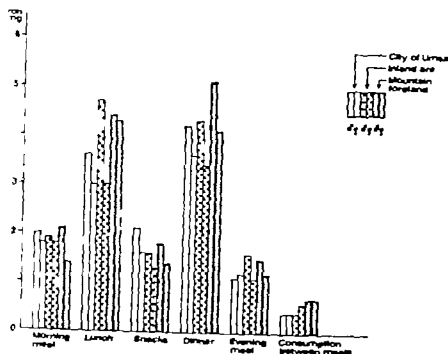


Fig 9 8-year-old group. Distribution of iron in mg in amounts consumed at different meals. Comparison between sexes and areas.

Calcium In all areas, the main part of the calcium content of the diet came from milk and milk products (Table 13)

Iron The average iron intakes for the groups at different meals are shown in Fig 9 On an average 4 mg of iron was supplied by lunch and dinner respectively in all areas. The boys as a group consumed more than the girls, and therefore had a higher iron intake (Table 22) The children in the mountain foreland had a higher iron intake in the amounts consumed at lunch in consumption between meals and in the entire daily consumption than did children in the city of Umeå.

In all areas about one-third of the iron came from bread and cereal products and one-third from the group meat, fish and eggs (Table 13).

Vitamin A thiamine riboflavin niacin and vitamin C The vitamins were obtained from roughly the same food groups in all areas (Table 13). About 20 per cent of the vitamin A was derived from β-carotene.

Vitamin D Children in the city of Umeå obtained the main part of the vitamin D in the diet from vitamin-enriched margarine and butter Only 19 per cent of the vitamin D consumed came from the group meat, fish and eggs. Children in the inland area obtained 41 per cent of the vitamin D in the diet from the group meat, fish and eggs, and 39 per cent from margarine and butter Children in the mountain foreland obtained 50 per cent of the vitamin D consumed from the group meat, fish and eggs, whereas 35 per cent came from margarine and butter The percentage distribution for the 8 year-old group as a whole is shown in Table 13

Table 14 *The composition of breakfast for 583 eight year-olds in different areas*

1=City of Umeå, 2=Inland area, 3=Mountain forland. The figures are percentages.

Type of breakfast	Area 1	Area 2	Area 3
Hot prepared breakfast	1	5	5
Gruel or gruel and sand ches	5	2	4
Porridge and milk, or porridge, milk and sandwiches	5	9	7
Cultured milk, prepared cereal or sandwiches	3	4	5
Milk, prepared cereal and sandwiches or sweet buns	22	15	15
Chocolate milk and sandwiches or sweet bun	32	31	30
Milk or chocola milk	1		
Tea and sandwiches and or sweet buns	15	16	24
Sandwiches	0	0	1
Soft drinks and sandw ches nd/or sweet buns	4	4	2
Coffee and sandwiches	1	3	0
Other such as soft drink or fruit	2	2	0
N bre kfast	9	7	5

C. *Composition of breakfast*

5—9 per cent of the children ate no breakfast whatever The most common breakfast con sisted of chocolate milk or tea, sandwiches and/or sweet buns (Table 14)

D *School lunches*

The energy intake was somewhat lower than the recommended dietary allowances for school lunches in Sweden (39). The nutrient content per 1000 kcal (4.2 MJ) is shown in Table 15 The mean nutrient content of con sumed school lunches was generally in accord ance with that recommended, with the ex ception of the high fat and somewhat low iron contents.

E. *General food habits*

The general consumption pattern, according to the food habit history for the entire 8 year-old group is shown in Fig. 10 The foods have been classified according to food groups. Only 16 per cent consumed vegetables daily

Table 15 *The 8 and 13 year-old group Mean daily intake of nutrients per 1000 kcal in school lunches*

Comparison h recommended dietary allowances for school lunches in Sweden

Age groups, area	N	Protein g	Fa g	Calcium g	Iron mg	Vit. A Retinol eq mg	Thia mine mg	Riboflavin mg	Vit. C mg
8 years									
City of Umeå	191	37	51	0 7	6.8	0 5	0.6	1.2	35
Inland area	171	37	53	0.7	7.0	0.6	0.5	1 4	33
Mou tain foreland	174	41	52	0.8	7 9	0 5	0.7	1 4	41
13 years									
City of Umeå	165	40	51	0.7	6 1	0.5	0.6	1 1	32
Inland area	170	38	55	0 6	6.7	0.5	0 6	1.3	30
Mountain foreland	218	43	51	0.7	7 7	1.3	0 6	1.6	42
Recommended dietary allowances		>25	27—38	>0.3	>8.0	>0.4	>0.3	>0.4	>20

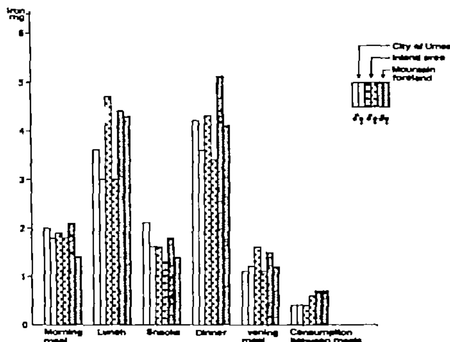


Fig 9 8-year-old group. Distribution of iron in mg in amounts consumed at different meals. Comparison between sexes and areas.

Calcium In all areas, the main part f the calcium content of the diet came from milk and milk products (Table 13)

Iron The average iron intakes for the groups at different meals are shown in Fig. 9 On an average, 4 mg of iron was supplied by lunch and dinner respectively in all areas. The boys as a group consumed more than the girls, and therefore had a higher iron intake (Table 22) The children in the mountain foreland had a higher iron intake in the amounts consumed at lunch, in consumption between meals and in the entire daily consumption than did children in the city of Umeå.

In all areas about one-third of the iron came from bread and cereal products and one-third from the group meat, fish and eggs (Table 13).

Vitamin A thiamine riboflavin niacin and vitamin C The vitamins were obtained from roughly the same food groups in all areas (Table 13) About 20 per cent of the vitamin A was derived from β-carotene.

Vitamin D Children in the city of Umeå obtained the main part of the vitamin D in the diet from vitamin-enriched margarine and butter Only 19 per cent of the vitamin D consumed came from the group meat, fish and eggs. Children in the inland area obtained 41 per cent of the vitamin D in the diet from the group meat, fish and eggs, and 39 per cent from margarine and butter Children in the mountain foreland obtained 50 per cent of the vitamin D consumed from the group meat, fish and eggs, whereas 35 per cent came from margarine and butter The percentage distribution for the 8 year-old group as a whole is shown in Table 13

Table 16b *Chi²-analysis of the homogeneity of the frequency of consumption in different geographic areas and age groups*

1=City of Umeå, 2=Inland area, 3=Mountain foreland. The figure 1, 2 or 3 after the *p*-value indicates the area in which the frequency of consumption was higher

Foods	Geographic areas	8 years *p*-value		13 years *p*-value	
Sausage	1 vs. 2	n.s.		n.s.	
	1 vs. 3	<0.001	3	<0.001	3
	2 vs. 3	<0.05	3	<0.05	3
Porridge	1 vs. 2	n.s.		<0.001	
	1 vs. 3	<0.001	3	<0.001	3
	2 vs. 3	<0.001	3	n.s.	
Gruel	1 vs. 2	<0.001	2	<0.001	2
	1 vs. 3	<0.001	3	<0.001	3
	2 vs. 3	n.s.		n.s.	
Prepared cereals, e.g. cornflakes	1 vs. 2	n.s.		<0.01	1
	1 vs. 3	n.s.			
	2 vs. 3				
*Bryta and/or *blöta	1 vs. 2	<0.001	2	<0.001	
	1 vs. 3	<0.001	3	<0.001	3
	2 vs. 3	<0.01	2		
Buns and cakes	1 vs. 2	<0.05	2	<0.01	2
	1 vs. 3	<0.05	3	<0.05	3
	2 vs. 3	n.s.		<0.05	2
"Palt"*	1 vs. 2	<0.001	2	<0.001	2
	1 vs. 3	<0.001	3	<0.001	3
	2 vs. 3				
Pancakes	1 vs. 2	<0.01	2	<0.001	2
	1 vs. 3	<0.001	3	<0.001	3
	2 vs. 3	<0.05	3	<0.001	3
Bread and butter	1 vs. 2				
	1 vs. 3	<0.001	3	<0.01	3
	2 vs. 3	<0.01	3		
Bread and margarine	1 vs. 2			n.s.	
	1 vs. 3	n.s.		<0.001	3
	2 vs. 3	<0.05	3	<0.01	3
Sweets	1 vs. 2	n.s.		n.s.	
	1 vs. 3	<0.001	1	<0.001	1
	2 vs. 3	<0.001	2	<0.001	2

*Bryta = thin bread broken into milk.
*Blöta = thin bread dipped in hot me   broth, or hot milk.
*Palt = heavy dumpling made of potato, barley or wheat flour and pieces of pork. It sometimes contains blood or liver.

Table 17 *Chi²-analysis of the homogeneity of the frequency of consumption in between-meal eating in different geographic areas and age groups*

1=City of Umeå, 2=Inland area, 3=Mountain foreland. The figure 1, 2 or 3 after the *p*-value indicates the area in which the frequency of consumption was higher

Foods	Geographic area	8 years *p*-value		13 years *p*-value	
Fruit	1 vs. 2	<0.01	1	<0.001	1
	1 vs. 3	<0.05	3	<0.01	1
	2 vs. 3	<0.001	3	n.s.	
Sweets	1 vs. 2	n.s.		n.s.	
	1 vs. 3	n.s.		<0.05	1
	2 vs. 3	n.s.		n.s.	
Buns and cakes	1 vs. 2	<0.001	2	<0.001	2
	1 vs. 3	<0.001	3	<0.001	3
	2 vs. 3	n.s.		<0.001	2
Soft drink	1 vs. 2	<0.01	2	<0.01	2
	1 vs. 3	<0.001	3	n.s.	
	2 vs. 3	n.s.		<0.001	3

potatoes, cheese, sausage, porridge and buns and cakes. They also drank coffee more frequently than the children in the city of Umeå.

Inland area vs mountain foreland. The frequency of consumption of vegetables, berries, fish, liver and cereal products was higher in the mountain foreland than in the inland area.

Frequency of consumption between meals (Table 17). Fruit was consumed more frequently by the urban children in comparison with the children in the inland area, who, on the other hand, more often consumed buns and cakes and soft drinks. There was no significant difference in the frequency of consumption of sweets.

Children in the mountain foreland had a more frequent consumption of fruit, buns and cakes, juice and soft drinks than children in the city of Umeå.

Comparison between the inland area and the mountain foreland showed only that fruit was consumed more often in the mountain foreland.

Foods liked In the city of Umeå the children named pancakes, spaghetti, macaroni sausage and meat loaf as the five foods most liked In the inland area the children most liked palt sausage, macaroni meat loaf and soup In the mountain foreland, palt sausage, pan cakes, meat loaf and macaroni were the best liked foods.

Foods disliked In the city of Umeå the children named brown beans, fish, pea soup liver and soup as the foods least liked. Children in the other two areas disliked about the same foods as the children in Umeå.

Sandwich consumption About half of the children in all areas consumed 3—4 sand wiches per day and roughly one-third con sumed 5—6 sandwiches daily 78 per cent of all the children named cheese as the most common sandwich filling. There was no dif ference between the areas.

III. 13 YEAR-OLD GROUP

The mean and median consumption according to 24-hour recall was greater for boys than for girls (Tables 18 *a* and 18 *b*) 13 year-olds in the mountain foreland consumed more than children in the inland area, who in turn consumed more than children in the city of Umeå. Significances of the sex and regional differences are shown in Table 22 and 23

A *Actual nutrient intakes in relation to recommended dietary allowances*

In all areas the average intakes of energy protein and calcium met or exceeded the recommended levels. Vitamin A, thiamine riboflavin niacin and vitamin C were above the recommended levels for both boys and girls. The average contents of fat iron and vitamin D however differed from the recommended amounts (Fig 11)

The fat content in the diets of the children in all three areas was above the recommended level (41)

The amount of iron in the quantities con sumed by the boys in the city of Umeå and in the inland area was slightly lower than

Table 18a. *The 13 year-old group Mean values and standard errors of the means of energy and some nutrients in food consumed according to 24-hour recall. Figures in italics are standard errors of the means*

Sex No.	Energy kcal	Energy MJ	Protein g	Fat g	Carbohydrate g	Calcium mg	Iron mg	Vitamin A Retinol eq. mg	Vitamin A β-carotene mg	Vit. D g	Thiamine mg	Riboflavin mg	Niacin eq mg	Vit. C mg
Boys	2668	11..	89	1 1	289	1495	16.7	1.5	1.7	4.2	1.5	2.6	27.7	78
305	*48*	*0.2*	*1.8*	*2.8*	*5.7*	*35*	*0.5*	—	—	*0.2*	*0.03*	*0.06*	—	*8.3*
Girls	2194	9.2	71	10	235	1..3	13.5	1.3	1.6	3 1	1.3	2.2	22.6	67
315	*36*	*0.2*	*1 4*	..	*4.5*	*9*	*0.3*	—	—	*0 1*	*0.03*	*0.05*	—	*2.8*
Total	431	10.2	80	111	6..	1364	15 1	1 4	1.7	3.7	1 4	2.4	..5 1	73
620	*30*	*0.1*	*1.1*	*1*	*3 6*	*3*	*0.3*	—	—	*0.1*	*0.02*	*0.04*	—	*4.3*

1 kcal=4.184 kJ (kiloJoule) 1 MJ (megaJoule)=1000 kJ
See note, Table 9a.

Table 18b. *The 13 year-old group Median values upper and lower quartiles of energy and some nutrients in food consumed according to 24-hour recall*

Sex No.	Per centiles	Energy kcal	Energy MJ	Protein g	Fat g	Carbohydrat g	Calcium mg	Iron mg	Vit. A Retinol eq mg	Vit. D µg	Thiamine mg	Riboflavin mg	Niacin eq mg	Vit. C mg
Boys 325	25th	2126	8.9	65	88	216	1084	11 4	0 7	[illegible]	1 1	1 9	18.8	40
	50th	2552	10.7	85	113	277	1444	15 0	1.0	3.3	1 4	2.5	25.6	59
	75th	3095	13.0	108	140	334	1864	19.8	1.3	4.6	1 8	3 1	34.2	84
Girls 315	25th	1731	7.3	55	75	179	894	9.5	0 6	1.8	0.9	1 6	16.1	36
	50th	2155	9.0	68	100	228	1193	12.4	0.8	2.6	1.2	[illegible]	1.0	51
	75th	[illegible]	10.7	84	121	282	1495	15.6	1 1	3.7	1.5	2.6	27.0	82
Total 620	25th	1889	7.9	60	80	196	988	10.6	0.7	1.8	1.0	1.7	17.3	38
	50th	2356	9.9	76	106	250	1292	13.5	0.9	[illegible]	1.3	[illegible]	23.2	55
	75th	2858	12.0	95	129	307	1682	[illegible]	[illegible]	4.2	1.7	2.9	30.5	83

the amount recommended. The boys in the mountain foreland had such a high total consumption that the iron content in their diet came up to the recommended amount. The girls iron intakes were from 64 to 81 per cent of the amounts recommended, highest in the mountain foreland.

In all three areas, the average amount of vitamin D supplied by the diet was below the level recommended. For children in the city of Umeå, the amounts of vitamin D in the diet for girls and boys varied between 26 and 33 per cent, for children in the inland area between 39 and 77 per cent and for children in the mountain foreland between 39 and 47 per cent of the recommendation.

B Distribution of nutrient intakes according to meals and contributions of different food groups

Energy The distribution of energy among different meals was the same as for the 8-year-olds, with no significant differences bet

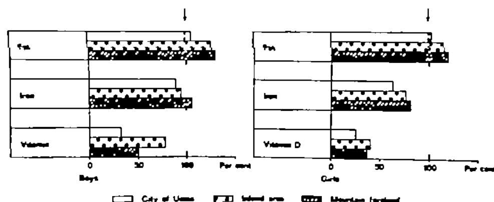
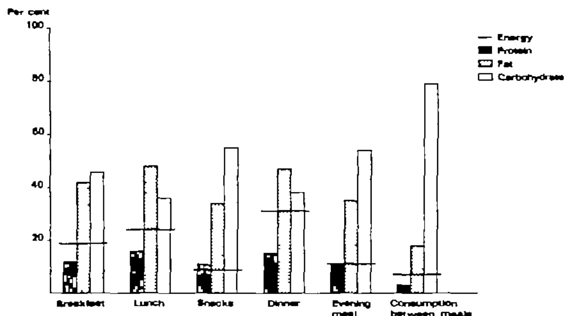


Fig 11 13-year-old group in different areas. Mean intakes of iron and vitamin D in per cent of the Recommended Dietary Allowances, USA, 1968 The mean intake of f is given in per cent of the mean recommendation proposed by the Swedish National Institute of Public Health. The arrow indicates the recommended level.



F g 12 13-year-old group grand total. Percentage distribution of energy among different meals during the day and the percentage distribution of energy among protein, f t and carbohydrate by meal

ween the areas (Fig. 12) On an average, 19 per cent of the energy intake was supplied by breakfast. The main supply of energy came from dinner 31 per cent. Only 6 per cent of the energy came from eating between meals, mainly sweets. About one-fourth of the energy came from milk and milk products (Table 19)

Protein The supply of protein was relatively evenly distributed among the day's meals (Fig 12) There was no significant difference between the areas. In all areas, 13 per cent of the total energy intake came from protein. Over 40 per cent of the protein in the diet came from milk and milk products (Table 19)

Fat The average fat content of the diet in all three areas was 42 per cent of the energy intake (Fig 12) In all areas, about one-third of the fat came from milk and milk products, one-third came from butter and margarine and one third from meat, fish and eggs (Table 19).

Carbohydrates Carbohydrates made up the main part of the snacks and between-meal consumption (Fig 12) For the 13 year-old group as a whole, 40 per cent of the carbohydrate consumed came from cereal products, about 20 per cent from sugar and candy (Table 19)

Calcium As for the 4- and 8-year-olds, the main part of the calcium in the diet came from milk and milk products (Table 19)

Iron Consumption of iron was higher in the inland area and the mountain foreland than in the city of Umeå. The boys, because of their higher total consumption, also had higher iron intakes at most meals (Fig. 13). In all areas, the iron in the diet came mainly from cereal products and from the group meat, fish and eggs (Table 19)

Vitamin A thiamine riboflavin niacin and vitamin C Children in all areas obtained the vitamins from roughly the same food groups (Table 19) About 20 per cent of the vitamin A was derived from β-carotene.

Vitamin D Vitamin D was supplied mainly by margarine and butter and by the group meat, fish and eggs (Table 19).

Table 19 *The 13-year-old group. Percentage distribution of total amount, energy and some nutrients among different food groups*

	Total amount	Energy	Protein	F	Carbohydrate	Calcium	Iron	Vit. A	Vit. D	Thiamin	Riboflavin	Niacin	Vit. C
Vegetables	2	0	2	0	2	1	3	1	0	2	1	2	11
Fruit and berries	8	3	1	0	7	1	3	1	0	5		3	36
Potatoes and root vegetables	9	5	4	0	11	2	9	5	0	13	3	16	22
Milk and milk products	45	26	42	28	16	87	6	20	8	25	67	8	24
Meat, fish and eggs	10	18	32	30		3	33	41	33	4	18	46	3
Cereal and cereal products	9	24	17	7	40	3	39	4	11	30	7	23	0
Butter, oils, margarine	2	13	0	32	0	0	0	28	48	0	0	0	0
Sugar and candy	15	11	2	3	22	3	7	0	0	1	2	2	4

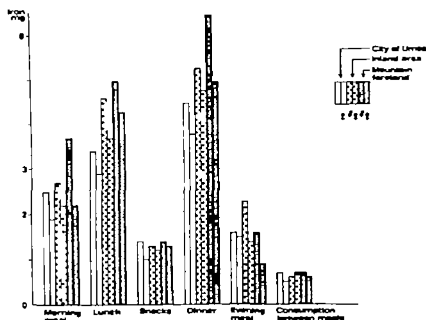


Fig 13 13-year-old group. Distribution of iron in mg in amounts consumed at different meals. Comparison between sexes and areas

C. *Composition of breakfast*

According to recall, 4—5 per cent of the children in all areas ate no breakfast whatever Hot prepared breakfasts were not eaten at all in the city of Umeå, but 8 per cent in the inland area and 12 per cent in the mountain foreland ate such a breakfast. The most common breakfast consisted of tea or chocolate milk and sandwiches and/or sweet buns (Table 20)

Table 20. *The composition of breakfast for 620 thirteen-year-olds in different areas*

1=City of Umeå, 2=Inland area, 3=Mountain foreland. The figures ar percentages.

Type of breakfast	Area 1	Area 2	Area 3
Hot prepared breakfast	0	8	12
Gruel or gruel and sandwiches	1	4	5
Porridge and milk, or porridge, milk and sandwiches	6	6	6
Cultured milk, prepared cereal or sandwiches	2	1	2
Milk, prepared cereal and sandwiches or sweet buns	20	17	7
Chocolate milk and sandwiches or sweet buns	28	28	34
Milk or chocolate milk	3	1	0
Tea and sandwiches and/or sweet buns	27	23	27
Sandwiches	2	1	0
Soft drinks and sandwiches and/ sweet buns	2	1	0
Coffee and sandwiches	4	3	2
Other such as soft drinks or fruit	1	2	0
No breakfast	4	5	5

D *School lunches*

The mean energy intake was below the recommended dietary allowances for school lunches in Sweden (39) The diet was satisfactory in relation to the recommendations with respect to all nutrients, except for a high fat content and a somewhat low iron content (Table 15).

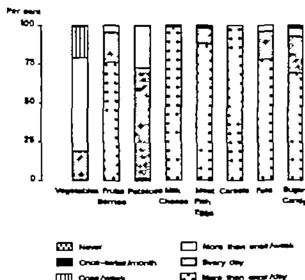


Fig 14 13-year-old group, grand total. Frequency of consumption of different foods classified according to food groups.

E. *General food habits*

The general consumption pattern for the entire 13 year-old group, according to the food habit history is shown in Fig 14 The different foods have been classified according to food groups. Only 19 per cent ate vegetables daily 95 per cent consumed fruit and/or berries daily 73 per cent ate potatoes. The other food groups were eaten daily by nearly 100 per cent About 95 per cent of the children consumed sugar and candy daily

Tables 16 *a* and 16 *b* present a comparative analysis of the frequency of consumption of different foods and dishes in different areas, according to the food habit history The Chi² analysis that was used is based on the same consumption frequency as for the 8-year-olds (p 26)

City of Umeå vs inland area Vegetables, fruit, cheese, liver and prepared cereals were more often eaten by the urban children. In the inland area they more frequently consumed berries, potatoes and cereal products. They drank coffee more often than the children in the city of Umeå.

City of Umeå vs mountain foreland The urban children had a more frequent consumption of fruit and sweets. In the mountain foreland they more often ate berries, potatoes, fish, blood pudding, sausage and cereal products. They also drank coffee more frequently than the children in the city of Umeå.

Inland area vs mountain foreland The children in the inland area more often consumed fruit, buns and cakes, and in the mountain foreland they more frequently ate vegetables, berries, cheese, fish, blood pudding and liver

Frequency of consumption between meals (Table 17) Fruit was eaten more often by the urban children in comparison with the children in the inland area. Buns and cakes, juice and soft drinks, on the other hand, were consumed more frequently by the children in the latter area.

Children in the city of Umeå had a more frequent consumption of fruit and sweets than children in the mountain foreland Buns and cakes were eaten more often in the mountain foreland.

Comparison between *the inland area and* the mountain foreland showed that buns and cakes were eaten more often in the inland area, soft drinks more frequently in the mountain foreland.

Foods liked In the city of Umeå, children named meat, palt meat loaf sausage and pancakes as the five best-liked foods. The 13-year-olds in the inland area preferred palt meat loaf macaroni meat and sausage. In the mountain foreland, palt sausage, brown beans, pancakes and meat were the best-liked foods.

Foods disliked 13-year-olds in the city of Umeå disliked fish, soup liver pea soup and fish balls. Roughly the same foods were also disliked in the inland area and the mountain foreland.

Sandwich consumption. In all three areas, about one-third of the children consumed 3—4 sandwiches per day about one-third consumed 5—6 sandwiches per day and roughly one-tenth consumed 7 or more per day

The most common sandwich filling was cheese In the city of Umeå, 59 per cent of the children named cheese as the usual sandwich filling, in the inland area 78 per cent, and in the mountain foreland 68 per cent. In the city of Umeå, 24 per cent usually ate sandwiches without filling, as did 7 per cent and 12 per cent in the two rural areas.

Median intakes of energy protein and fat per kg body weight

Table 21 shows that the intakes in relation to body weight were higher in the 4 year-olds in comparison with the 8 and 13 year-olds.

Table 21 *4-, 8 and 13 year-olds' median intakes of energy protein and fat per kg body weight*

	Energy kcal/kg	Protein g/kg	Fat [illegible] g/kg
4 years			
Boys	100	3 4	4 3
Girls	88	3 1	3 7
Total	94	3 3	4 0
8 years			
Boys	85	2 8	3 5
Girls	73	2 4	3 2
Total	81	2 6	3 6
13 years			
Boys	56	1 9	2 5
Girls	45	1 4	2 1
Total	51	1 6	2 3

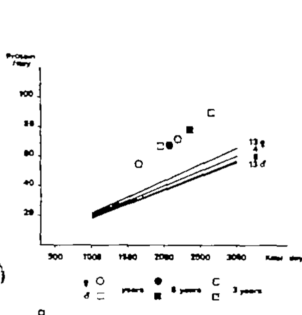
Mean nutrient intakes in relation to the energy consumption

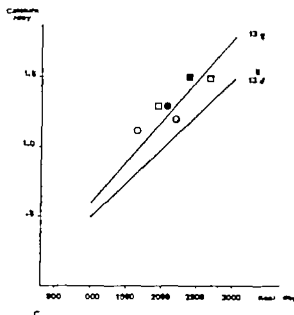
In Figs. 15 a—t the nutrient content diets consumed by 4 8 and 13- [illegible] shown in relation to the U.S [illegible]

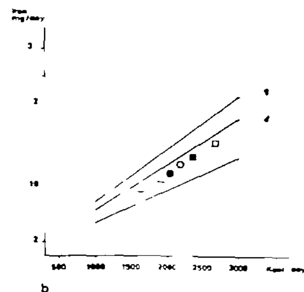
dietary allowances, (19) calculated as recommended content of the respective nutrient per 1000 kcal (4.2 MJ) Protein, calcium, iron, thiamine and niacin intakes were well correlated to energy intake. For all age groups, the protein content of the diet was clearly above the recommended level Iron intake was below the recommended amounts except for 8 year olds. The iron content of the diet per 1000 kcal (4.2 MJ) varied between 5 8 and 6.3 mg The dietary supply of vitamin D was low for all age groups and both sexes. The content of vitamin D in the diet per 1000 kcal (4 2 MJ) varied between 1 3 and 1 6 μg

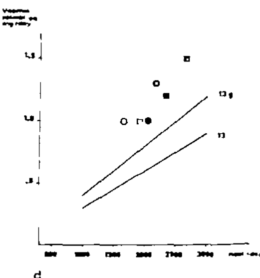
Comparison between the sexes and between the different areas in median energy and nutrient intake

According to the 24-hour recall the boys generally consumed more than the girls. Especially among the 8 and 13 year old children in the rural areas, significant differences bet









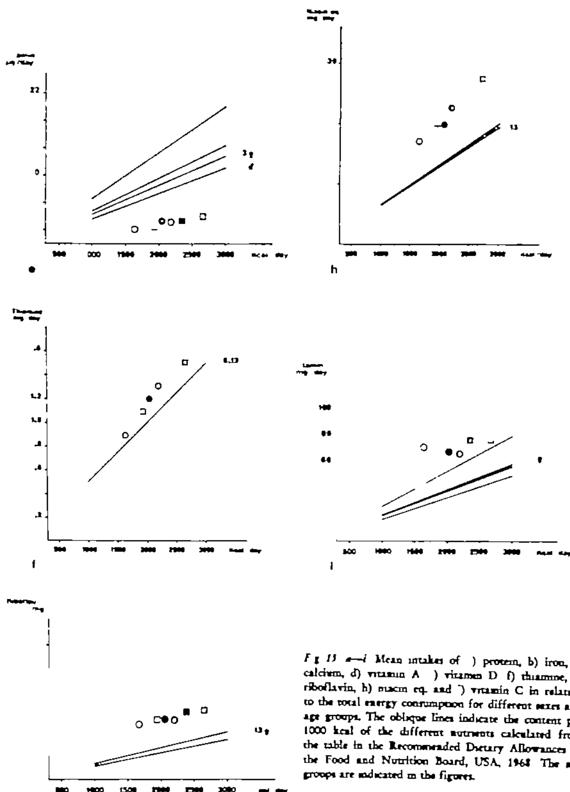


Fig 13 a—i Mean intakes of) protein, b) iron,) calcium, d) vitamin A) vitamin D f) thiamine, g) riboflavin, h) niacin eq. and) vitamin C in relation to the total energy consumption for different sexes and age groups. The oblique lines indicate the content per 1000 kcal of the different nutrients calculated from the table in the Recommended Dietary Allowances of the Food and Nutrition Board, USA, 1968. The age groups are indicated in the figures.

Table 22. *Significances of the sex differences in median energy and nutrient intake in different age groups and areas*

A significant difference means that boys had higher median intake than girls.

	Energy	Protein	Fat	Carbohydrate	Calcium	Iron	Vit. A	Vit. D	Thiamine	Riboflavin	Niacin	Vit. C
4 years												
City of Umeå												
Boys vs. girls	*	*	*	**		*	*		*		*	
8 years												
City of Umeå												
Boys vs. girls	**			*		*			**			
Inland area												
Boys vs. girls	*	**	**		*	**			**	*	***	
Mountain foreland												
Boys vs. girls	**		**	**	*	* *			**			
Total												
Boys vs. girls	* *	*		**		*	**	*	***	**	***	
13 years												
City of Umeå												
Boys vs. girls	**	*		**		*			*			
Inland area												
Boys vs. girls	***	***		***	**	**	**		**	**	*	*
Mountain foreland												
Boys vs. girls	*				**	**	**		*	***	*	
Total												
Boys vs. girls	* *	* *	**	*	***	* *	**	**	***	*	**	

*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$

ween the sexes in median energy and nutrient intakes were found (Table 22).

The children in the inland area and the mountain foreland consumed more than the urban children. The differences were most accentuated between the children in the city of Umeå and the mountain foreland for both 8- and 13-year-olds (Table 23).

Cross-checking between recall and the food habit history

The consumption of foods which according to the food habit history were consumed daily was classified according to food groups. The classification shown in Fig. 5 was used. The data in the food habit history were compared with those in the recall for the same child in order to see whether the food groups which according to the food habit history should have been represented daily in the diet were also included in the recall. It was found that there was correspondence with respect to all food groups except fruit, vegetables and potatoes. At least one of these food groups was lacking in the recall for 20 per cent of the 4-year-old group and for 9 and 16 per cent of the 8- and 13-year-old groups respectively.

Table 23 *Significances of the regional differences in median energy and nutrient intake for 8 and 13-year-olds*

1 = City of Umeå, 2 = Inland area, 3 = Mountain foreland.
The differences in median intake between the areas generally followed the pattern Are 2>1 3>1 and 3>2.

	Energy	Protein	Fat	Carbohydrate	Calcium	Iron	Vit. A	Vit. D	Thiamine	Riboflavin	Niacin	Vit. C
8 years												
1 vs. 2												
Boy	***	**		*							*	
Girls	**											
Total	**			*					**			
1 vs. 3												
Boys	**	**	***	**	***	*		**	**	**		
Girls	***	**	*		*		***	**	**	*	*	
Total	**	**	**	***	**	**	**	***	***		**	
2 vs. 3												
Boys												**
Girls		**										
Total										*		
13 years												
1 vs. 2												
Boys	**											
Girls												
Total												
1 vs. 3												
Boys	**	**						**			**	
Girls								**			*	
Total			**	**		**	**	**	**		**	
2 vs. 3												
Boys									*			
Girls		**							**			
Total		**						***	**	**		

*p<0.05 p<0.01 *p<0.001

DISCUSSION

1 *Interview methods*

With the two methods of dietary investigation used in this study the 24-hour recall and the food habit history both nutritional intake and food habits were investigated. Pekkarinen (30) and others have shown that 24-hour recall is a suitable method for determining the nutritional intake of groups of adults. Within the framework of this study 8 and 13-year olds proved to be able to give an acceptable picture of their consumption of a school meal on a group basis, as shown by weighing and nutrient analysis of double portions (33) The accuracy of the information about consumption at other meals during the day is difficult to evaluate but there is no reason to believe that such information should be less accurate. Furthermore, breakfast, the afternoon snack and the evening meal were so similar from day to day for all age groups and in all areas that there should have been little difficulty in recalling their composition. In order to check the accuracy of the information about food consumption obtained from the children and

to obtain supplementary data it was necessary to interview the mothers. This supplementary interview is especially important in regard to dinner because children generally do not know the method of food preparation. Therefore although information provided by the mothers is also a source of some uncertainty and cannot be checked, this type of combined interview is important in all dietary studies on children below the age of 12—14 years (6) Information about consumption between meals or away from home can only be provided by the child Older children should be assured that the information is confidential, otherwise part of the between-meal consumption of sweets may be concealed (6) In this study therefore, the 13 year-olds were interviewed separately before the interviews with their mothers

There is reason to suspect that some of the information about the children s consumption was exaggerated. The results of cross-checking between the recall and the food habit history (p 36) suggest that the mothers, perhaps unconsciously presented the children s consumption habits as 'better' than they actually were, especially with respect to the consumption of fruits and vegetables It should be noted however that the two methods measure different aspects of food intake. Agreement between the results of the two methods is rather good, since absolute precision can never be achieved in surveys of this kind. The weighing method is the only one that gives an absolutely precise measure of food intake. However it is practically impossible to use this method in larger field surveys without the risk of influencing the results In the present study as in other studies in which the 24-hour recall has been used it can be assumed that individual errors in the estimation of food consumpt on will be levelled out on a group basis A areful inter iew technique especially in regard t est mates of amounts is nonetheless necessary A ording to Beal (6) the use of 24 hour ntakes as the sole basis for calculation may be justif ed in group surveys but they are inadequate for individual studies The results of the methodological study of the recall technique (33) in the present investigation support this statement.

2. *Nutrient intake*

In all the age groups studied and in the three areas investigated the mean values for nutrient intake were generally satisfactory in relation to recommendations. The exceptions were iron intake in the 13 year-old group and the intake of vitamin D which were low in all age groups. In evaluating these findings it is important to remember that the recommendations are intended to serve as goals for planning food supplies and as guides for the interpretation of food consumption records of groups of people (19) Furthermore, malnutrition does not occur if the recommendations are not completely met. It is also important to consider that there may be upper limits of desirable intake e.g. with respect to fat.

It should be noted that the median values for some nutrients, e.g. iron and some vitamins were lower than the corresponding means. These differences are due to the inclusion in the recalls of a number of meals rich in iron (blood pudding) and in vitamins A, D (liver) and C (berries) Even a few recalls that included such meals increased the mean values for the group thus the medians for these nutrients are more truly representative of the group intakes. If the median values are used instead of the means and related to the recommendations, there is accentuation of the fact that the iron content of the diet for the 13 year-old group and the content of vitamin D for all age groups were below the recommended levels. The intake of the other nutrients calculated was satisfactory in relation to the recommended levels in the clinical investigation, no signs of nutritional deficiency were found (34) which also suggests that nutritional intake was adequate. However the methods used in the clinical examination are rough.

The energy intake of the 4 year-olds was approximately the same as that reported by Bransby (10) and Widdowson (46) in England, but higher than the total energy intake reported in the Health Departments Survey in England (28), and in earlier studies from the USA (4) In comparison with later studies from the USA (12) the difference in energy intake is small For the 8 and 13-year-olds, the energy intake was about the same as that reported by Widdowson (46) and Burke (12). The total energy intake was about the same as that reported in a Swedish food consumption investigation from the early 1960 s by Sterky (42). However there was a difference with respect to energy intake per kg body weight, probably reflecting variations in growth and physical activity Of course, all comparisons between the present study and other studies must be made with reservations for differences in methodology

In spite of having a higher average energy intake, the children in the mountain foreland had lesser skinfold thicknesses than children in the city of Umeå. In all age groups, boys had lesser skinfold thicknesses than girls (34). The regional differences presumably reflect the effect of greater physical activity on the part of the rural children. A direct analysis of the possible connection between recall data and anthropometrical data was not possible, since the recall method does not permit individual comparisons.

Regarding the fat content of the diet, our present knowledge does not permit speculation as to the possible long term risks for children who consume a diet with a constantly high level of fat. Other nutritional studies of children in Western Europe and the USA have shown about the same proportion of fat in the diet (4 11 14 22, 23 42)

A striking feature was the high frequency of carbohydrate-rich between-meal consumption mainly of sweets, cookies, cakes and sweet buns. This consumption was insignificant from the standpoint of nutrient intake, both as a source of energy and as a source of nutrients (Figs. 4 8 and 12) It was possible to correlate a high frequency of consumption of sweets, sweet buns and cakes with higher caries indices among the investigated children (35) Only 17 per cent of the 4 year-olds were caries free and only 0 4 and 0 per cent of the 8 and 13 year-olds respectively (36)

It is clear from this study that milk plays a central role in the diet of Swedish children. Thus results in a very high protein intake above all in the 4 year-old group. A correspondingly high protein intake was found by Debry et al (14) for French children aged 18 months to 3 ½ years by Crumrine et al (13) in preschool children in the USA and by Bresard (11) in school children in France Lower levels of protein intake were found in American and British investigations in the 1950 s (4 10 46). The protein content of the diet is clearly higher than necessary This finding deserves comment. According to Fomon (18) the average protein requirement in infants in the age groups 0—2 months and 1[illegible] months is no greater than 2 1 and 1 2 g/kg/day respectively There is no reason to believe that the req[illegible] is hi[illegible]her later in life when the rate of growth is much less If milk comes to d[illegible] the diet there may be a risk of the child[illegible] developing iron deficiency anaemia [illegible] consumption of food [illegible] to low consumption of foods with a [illegible] content (47)

Iron intake from the diet [illegible] from iron-enriched f[illegible] the 4 and 8-year [illegible] was satisfactory [illegible] these groups was [illegible] deficiency anaemia [illegible] for the 13-year [illegible] dations. In this [illegible] deficiency anaemia [illegible] The direct cause [illegible] but massive loss [illegible] These cases [illegible] anaemia is to be [illegible] cessive menstr[illegible]

contain sufficient amounts of iron. As previously shown by Blix (8) individuals who have a low energy consumption run the greater risk of becoming iron-deficient, because there is a close correlation between the energy and iron contents of food. The diet that the investigated children consumed was qualitatively about the same as the average diet in Sweden, characterized by a relatively low content of iron. In 1965 this diet contained 5 7 mg iron per 1000 kcal or 4.2 MJ (47) that is, about the same as in the present study (5 8—6.3 mg) Since the children in this investigation had a relatively high energy intake and a high consumption of iron enriched bread, their total average iron intake was in accordance with or above that recommended with the exception of the 13 year-old group The percentage of iron that was of true animal origin cannot be stated. Layrisse et al. (24) have shown that dietary iron from foods of animal origin is best absorbed. The upper limit for iron absorption from cereals and vegetables was set at 10 per cent, for meat at about 30 per cent. This should be kept in mind when the recommended dietary iron intake is discussed. An expert group appointed by FAO/WHO (17) in 1970 therefore proposed that the recommended iron intake should be adjusted in relation to the type of diet habitually consumed, in view of the differences in iron absorption from different foods. This means that in the future, calculations of the adequacy of iron intake should take into consideration the proportion of animal foods in the total energy supply

No clear relationship between iron intake and haemoglobin level was found either in this study (37) or in that of Beal (5)

In all age groups and in all areas, the content of vitamin D in the diet was low in relation to the recommendations of the Food and Nutrition Board Other investigations of the vitamin D content of the Swedish diet have shown the same [illegible] 0) No rickets or post-rachitic stat[illegible] found in the clinical investigation [illegible]34 36) Vitamin D enrichment of commercial infant formulas and the administration of vitamin D supplements to nearly all infants and children below the age of 3 years has made rickets a rare deficiency disease in Sweden. Besides being supplied by the diet, vitamin D is synthesized by ultraviolet irradiation of precursors in the skin An expert group appointed by FAO/WHO in 1970 (17) proposed a reduction of the daily recommended level for children 7 years of age or older to 2 5 microgram which would be on the level of the vitamin D content of the diets in this investigation. For children under the age of 7 years, it was proposed that 10 micrograms be retained as the recommended daily intake This level was not met by the diet of the 4-year-olds in this investigation It is impossible to know whether the recommendation actually was met through the addition of the effect of sunlight and the fact that many of the children also received vitamin D supplements. The supply was probably satisfactory because no deficiency state was found. It is hardly possible to meet the current and proposed recommended level by diet alone since there are few good dietary sources of vitamin D

It was clear in all age groups and in all areas that the boys consumed more than the girls and thus had higher intakes of energy and nutrients These findings are in accordance with those of other investigators (42, 46)

3 *Different meals*

The pattern of meals during the day was relatively uniform, especially in the rural areas. With respect to both nutrient content and its general composition breakfast for most of the children was of about the same type as that found in studies from other parts of Sweden by Enell (15) and Arvedson et al. (3) It is of particular interest, however that in the present study the breakfast frequently consisted of sweet buns. There was a tendency for more complete breakfasts to be eaten in

the rural areas in comparison with the city of Umeå, perhaps on account of more traditional food habits.

The school meals, which were of the same type in all areas, generally met the Swedish recommended dietary allowances for all nutrients, except for energy fat and iron content. Other studies of school lunches in Sweden have shown the same results (38) Energy requirements, however are hard to estimate because of the great individual variation and the variation in physical activity The fat content in the school lunches was as high as in other comparable studies in Sweden (42) Concerning the iron content in the diet, it is to be observed that the values given are mean values. The corresponding median values lie about 1 mg lower e.g. at the same level as in the general Swedish diet, calculated per 1000 kcal. In this connection, it should be emphasized that school lunches should not only fulfil nutritional requirements, but should also be a means of teaching children correct food habits. Thus, preparing nutritionally correct lunches in an appetizing way and serving them in an attractive setting has a pedagogic function. Schools should pay more attention to this aspect of the school lunch and also provide more information about general nutritional principles at different school levels.

4 *General food habits*

Finally attention should be drawn to the differences found in the frequency of consumption of different foods according to the food habit history The differences were mainly found between the urban and the rural children. The somewhat one-sided consumption of milk and cereal products that was found, especially in the two rural areas, is partly similar to the diet described by Odin in his investigation of the same area in 1929—31 (29) He stated that there were three different types of diets in the county with different types of transitions from one area to another In the coastal area, the adult population consumed a lacto-cereal diet. Cereal products, milk, barley gruel and porridge, potatoes, crispbread and herring formed the common diet. Farther inland, where the population was mainly engaged in forestry the predominant diet consisted of pork, meat, palt and bread In the mountain areas, the diet also included fish, due to the abundance of fish in the mountain lakes. In the towns there was a third type of diet, which was more varied but which had a lacto-cereal base Among school children, the lacto-cereal diet predominated in all areas, but the adult diet in the different areas naturally also influenced what was served to the children. In all parts of the county the diet at that time rarely contained fruit or vegetables.

The type of diet that children consume today 40 years after Odin's investigation, shows clear changes in composition, but a diet rich in milk and cereal products is still present, mainly in the rural areas. The consumption of fruit has increased, but the frequency of fruit consumption is higher in the city of Umeå and in the mountain foreland, with its larger villages, than in the inland area, which is almost completely rural. Berries and potatoes are consumed more often in the inland area and in the mountain foreland compared with the city of Umeå, probably due to the fact that there is easier access to these foods in these areas. Common to all areas is the fact that vegetables are fairly rare in the diet. This appears from both the food habit history and the 24-hour recall.

It is interesting to cite a figure from Odin's investigation with respect to coffee consumption. He stated that 74 per cent of school children drank 1—3 cups of coffee daily In the present investigation, the amounts of coffee consumed were not recorded, but coffee drinking is plainly more common in the rural areas than in the city Thus, like the prevalence of milk and cereal products can be interpreted as an expression of the fact that traditional habits persist longer in rural

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 215 1971

A STUDY OF THE MENTAL HEALTH OF THE NEAR RELATIVES OF TWENTY MULTIHANDICAPPED CHILDREN

BY SHEILA MARGARET BERGGREEN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

OMTALE I DAGSPRESSEN FRABEDES!

ACTA PÆDIATRICA SCANDINAVICA
Supplement 215 1971
From The Children Hospital in Vangede
(Physician-in-charge: Dr Jørgen Lanstrup)

A STUDY OF THE MENTAL HEALTH OF THE NEAR RELATIVES OF TWENTY MULTIHANDICAPPED CHILDREN

by

SHEILA MARGARET BERGGREEN
M.B. Ch.B.

DENMARK 1971

CONTENTS

Introduction	5
The present investigation	7
Description of material	7
Table I. Extent of handicap in children	8
Case histories	9
Figure 1. Case 1	10
Comments and discussion	16
Table II. Mental health of relatives	20
Numerical assessment of results	21
Proposals	22
References	24

Introduction

The presence of a handicapped child in a family has provided many authors with raw material and the subject has been treated with sentiment or stark realism. In his Christmas Carol, *Charles Dickens* (5) depicted the clinical picture of Tiny Tim. The Cratchett family consisted of six children of whom Tiny Tim was one of the youngest. Tiny Tim appears to have had a hemiplegia as suggested by his withered hand and the facts that he walked with a crutch and his limbs were supported by an iron frame. His mental development is depicted as normal or nearly so as he was able to express his abstracts thoughts in words and to sing well. The family was poor there was no welfare state, but this handicapped child is described, nevertheless, as being surrounded by helpful siblings in a happy family circle with both parents taking active parts in his care. It is, however suggested that the ultimate prognosis for Tiny Tim was poor

Other authors, notably *Pearl Buck*, who writes from personal experience have analysed the problems involved in the adaptation of the family structure to the presence of a mentally retarded child. Pearl Buck has considered these problems in several different environments, in precommunist China, in modern America and in her own personal case, in which, after many deliberations, institutional care had to be resorted to. (2, 3, 4)

In his provocative play *A day in the death of Joe Egg, Peter Nichols* (20) has dramatized the subject and brutally exposed the stresses to which the parents of a mentally retarded spastic child are subjected and the diversity of advice and comments made by friends, relatives and the medical profession.

The subject has also been dealt with scientifically by a number of authors who have studied the repercussions on the other family members of a mentally handicapped child (13, 18, 19 21, 22) In 1963, *Carolyn M Fowle* (13) from California U.S.A., found that the presence of a mentally retarded child in the home did not have any adverse effect on marital integration but that siblings, particularly the oldest female sibling, might be exposed to considerable stress when a retarded child was kept at home She concluded, therefore that the welfare of siblings should be considered when counselling parents of severely retarded children. In 1967 a working party in Britain published a report on stress in families with mentally handicapped children. (19) In this, they quote a table from an unpublished work by *Holt* concerning various investigations of the effects on family life of children with mental retardation due to different causes. Considerable emotional and practical difficulties are seen to arise parents particularly the mother may become exhausted, families disturbed and siblings affected. About half of the mentally retarded children involved in these investigations were mongols who are probably the easiest type of retarded child to keep at home so the widely divergent figures quoted probably represent minimum figures for mental deficiency taken as a whole. A monograph by *Tizard and Grad* in 1961 (22), again from Britain, surveys the entire problem from different angles and particularly stress is paid to the role of the medical profession and the importance of the first approach. In a recent article from Finland, *Maija-Liisa Koski* in 1969 (17) described what she appropriately terms the coping processes in childhood diabetes i.e. the methods the parents and families adopt in caring for children with a chronic somatic disease. Two Danish authors, in 1970, *Friis & Scheel Thomsen* (12), were struck, in a follow-up investigation of mentally retarded criminals, by the abnormality of the family situation in a great number of cases. Numerous other authors have touched on the problem and it has not proved possible in the time available to quote more than a few *Stella Stillson Slaughter* in 1960 discusses many of the problems with which parents of mentally retarded children are faced (21) *John G Ho-*

cells in 1963, although not dealing directly with mental deficiency emphasizes the concept of the family as a dynamic entity and outlines therapeutic consequences and possibilities of family psychiatry (15) A Danish school doctor in a recent series of articles on *Risk Children* (7–11) has undertaken a comprehensive follow up examination of children considered to be at risk on account of a variety of factors in their early lives and backgrounds.

Everyone working with mentally retarded children must, at one time or another have been struck by the number of peculiarities in their family backgrounds. The presence of a handicapped child in a family results in states of tension affecting all of the family relationships and these must be experienced even by the psychologically most robust. The author who is *not* a psychiatrist has been struck by the abnormal lives which the normal siblings are forced to live. The present position could possibly be improved by increasing facilities for inpatient treatment of the handicapped child. Several other cases have recently been observed in which inpatient care of the handicapped child has saved the family as a functional unit although an intermediate period of adjustment may be necessary

The Present Investigation

This investigation concerns a limited group in multihandicapped patients in present-day Denmark and it appears, therefore, desirable to describe local conditions briefly A description of *Service systems in Denmark* is avail able in pamphlet form (1969) (6) and conditions in this hospital are to be found in another descriptive pamphlet (1) and in an unpublished work by *Therese Halskov* (1968) (14) who also investigates the effects on the patient-parent relationship of a number of socio-economic factors, (in this instance, how ever inpatients were concerned) In Denmark the National Health and Social Security Ser vices are thus well-developed. There are, how ever contrasts. Families are smaller mothers go out to work, life is more hectic, poverty is not acceptable, the standard of living is high and a great deal of financial and material assistance is expected from the public authorities and is accepted as a right. The vital prognosis for the handicapped child is infinitely improved since Dicken s time. These children thus continue to be a burden on their families of the community for many years. They increase in size but the improvement which can take place in their physical and mental development is still limited.

The initial impact of a handicapped child on a family comes as a stunning blow which tries the resources of the family and threatens their integrity The problem is a dynamic one and continues to exist for as long as the child lives and it influences and modifies the lives of all of the family members concerned. It cannot be solved once and for all. The parents receive a great deal of advice, much of which is unsolicited. Well-meaning friends and relatives will advise them "to send the child away or will give controversial advice about the daily care and nursing Tensions and feelings of guilt are, therefore inevitable. Both of the parents do not necessarily have the same opinion. The mother is apt to devote herself to the immediate needs of the sick child to the exclusion of everything else so that the other children, her husband and her own mental and physical health suffer Marriages and family life are threatened.

The present study emphasizes particularly a further group of children at risk, viz the normal siblings of multihandicapped children. The needs of the sick children sap the physical and mental energies of the parents so that the reserves left for their normal children are naturally limited, however good their intention may be

Material

The material consists of 20 patients (11 boys and 9 girls) aged 3½-15 years receiving day care in the Department for Cerebral Palsy of the Children s Hospital.

All of the children concerned are mentally retarded and all have some form of motor handicap necessitating various orthopaedic appliances ranging from special footwear crut ches, splints to wheel chairs and walking aids. Many of them have epilepsy Few of them are continent and many of them salivate so profusely that this is almost as great a problem. A great proportion of the children are unable to express their needs in speech. Very few of them are able to feed or dress themselves without help. Several of the children wear glasses on account of strabismus or other forms of defective vision and one has a hear ing aid. None of the children present any form of severe behaviour disturbance.

These children all live in their homes. They attend this department from 9 a.m. to 3 p.m. and special transport from their homes is provided. During their day in hospital, they re ceive physiotherapy nursery school and/or school training, according to age and ability and this includes speech therapy where this is considered necessary For part of the day they join the normal activities of the wards for spastic children to which they are attached. They receive a midday meal and an afternoon

Table 1. Schematic presentation of the extent of the physical and mental handicap in 20 children receiving day care. The number of crosses in the four columns: epilepsy, degree of immobility, incontinence and salivation, provide a rough indication of the amount of work involved in their care.

Number	Age	Sex	Approx. Q.	Epilepsy	Degree of immobility	Incontinence	Salivation	Speech	Independence	Patient's basic mood	Placing in Family	DIAGNOSIS
1	10	M	<20	+	+++	+++	+	0	0	5/5	Unhappy	Tetraplegia, caries, otitis media, strabismus
2	5	M	65	+++	++	++	—	Excellent	+	2/3	Neutral	Tetraplegia, strabismus
3.	10	M	75	—	++	—	—	Excellent	+	1/2	Neutral	Progressive muscular dystrophy
4.	3½	M	<20	+++	+++	+++	—	0	0	4/4	Neutral	Tetraplegia, anocmia
5.	10½	F	43	—	+	—	—	Excellent	+++	1/2	Happy	Tetraplegia, athetosis, hypermetropia, strabismus
6.	1½	M	<20	+++	+++	+++	—	0	0	2/2	Neutral	Diplegia, strabismus
7	12½	M.	50	—	+++	++	+++	Unintelligible	0	3/3	Happy	Tetraplegia, athetosis
8.	8	M	<20	+	—	++	++	0	+	3/3	Happy	Choreoathetosis, contact dermatitis
9.	14	F	70	—	++	++	—	Excellent	+++	1/4	Neutral	Spina bifida, hydrocephalus, flaccid diplegia, pyelonephritis
10.	11	F	48	—	+	+	—	Unintelligible	++	2/2	Happy	Hemiplegia
11	10½	F	42	—	++	—	—	Fair	+	1/3	Neutral	Hydrocephalus, tetraplegia, myopia
12.	9½	M	<20	++	++	+++	+++	0	0	4/4	Neutral	Tetraplegia, athetosis
13	12	F	<20	—	++	+++	+++	0	0	1/2	Happy	Tetraplegia
				—	++	—	—	Excellent	++	3/4	Neutral	Tetraplegia, myopia
				—	+++	+++	—	0	0	2/2	Happy	Hydrocephalus, tetraplegia, cong. heart disease
				++	++	+++	+++	0	0	1/2	Neutral	Hydrocephalus, strabismus
				++	+	++	+++	0	++	1/2	Happy	Hemiplegia
				++	+++	+++	+	0	0	3/3	Happy	Athetoid paraplegia
				—	+++	+++	+++	0	0	2/2	Neutral	Microcephaly tetraplegia
				—	+	—	—	Limited	+++	2/4	Happy	Triplegia, ataxia, deafness

snack before being returned to their homes. As each of the special ambulance-cars takes a complement of seven children, the journey in each direction may last for as long as one hour The daily activities outside their homes may thus last from approximately 8 a.m. to 4 p. m. from Mondays to Fridays.

Officially only 12 places are available for day care patients. These 20 patients have been accomodated by the facts that some wards have offered to take an extra patient, two wards which had not previously had day care patients have taken one and two patients, respectively and, in a third ward two places have each been divided between two patients so that one child comes three days weekly and another two days. This latter arrangement is regarded as an emergency measure only as it complicates the routine arrangements for physiotherapy schooling, transport etc.

This particular group of children was chosen for investigation because it is the group in which the author is best acquainted, not only with the children but also with their families and their problems. The children are seen daily in the wards, nursery schools and physiotherapy department. Their parents are seen at parents meetings, social events, interviews and orthopaedic consultations and many of them are contacted at intervals by telephone. Each child has a notebook in which messages to and from home can be recorded. A psychiatric social worker visits the homes regularly Other information was collected from the case histories, physiotherapists, the ward staffs, teachers from other hospital departments and from the ambulance drivers who form a vital connecting link between hospital and home.

The following data are recorded in Table I for each of the patients· Name, sex, and case number age of the child in January 19"0 The presence and degree of epilepsy immobility incontinence and salivation are indicated by crosses. The ability of the child to communicate in speech is recorded. The placing of the child in the family is of importance. For this purpose stillbirths and neonatal deaths are ignored. In one family the father had two adult children in a previous marriage. As these are now independent, they are also ignored in the present survey As it was considered that the basic mood of the child might influence or reflect the family situation, an attempt was made to summarize this under the headings. Happy neutral or unhappy Similarly the independence of the child has been indicated by crosses. The main diagnoses are also tabulated to give an impression of the degree of handicap.

Each case history is briefly reviewed and an attempt is made to assess the various factors which can be of significance for the mental and physical well-being of the family are recorded. These include the ages and occupations of the parents, an impression of the home, the number and type of orthopaedic devices, the ages of the other siblings and any deviations from normal which they show An attempt is made to portray the situation as it presented itself in January 1970 with the practical problems involved. For the purpose of this article, the etiology and finer aspects of differential diagnosis are ignored.

1 Boy ged 10 years. He is the fith of five siblings and seven years younger than the youngest sister. The father is an artist and the family live rather bohemian life. Both parents are 53 years old. The child has an intelligence quotient of less than 20 and has very severe spastic tetraplegia, epilepsy strabismus and nystagmus. The condition appears to be progressive and the diagnosis may be revised. The child is completely helpless and incontinent. Feeding is very difficult and time-consuming on account of reverse swallowing. Inpatient treatment has been offered on numerous occasions and refused. Orthopaedic operation (adductor tenotomy) has, similarly been refused. The child has purulent otitis media with ulceration on the pinna suspected of being malignant and advanced caries. He has bilateral drop foot with scissoring of the legs, asymetric torsion spasm, asymetric tonic neck reflex. He has some movement of the head and eyes but no speech. H is unable to hold anything in his hands.

Remarks: This child has lived at home until autumn 1900 and the various members of the family have all participated in his care. The older siblings

have now begun to leave home, the father's health is failing and the mother feels neglected and bitter The child has been given a great deal of affection and handling but his somatic needs have been grossly neglected. The mother has persistently refused in-patient treatment and demanded a nursery school place. This has been attempted but will now have to be abandoned. The child undoubtedly enjoys company and music but cannot himself participate in any activities. The mother is resentful, critical and uncommunicative A sister aged 17 has shared a room with the boy and attended to his needs at night. Two sisters are now working with handicapped children.

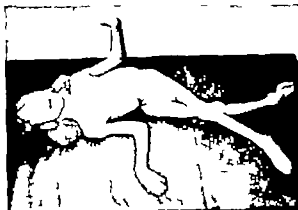




Figure 1. *Case 1 showing deformities caused by muscular spasm and contractures and asymmetric tonic neck reflex*

_ Boy aged five years. He is the second of three siblings. The sister aged eight and brother aged three years are healthy The father is photographer and the mother was photographer's assistant prior to marriage and now a part-time job in a nursery school. The father is 3_ and the mother 78 years of age. The child has an intelligence quotient of about 65. He has spastic quadriplegia, epilepsy strabismus and reduced ision. His motor handicap is severe but he has excellent speech. He requires support while sitting, can crawl alone, can ride a special tricycle and walk with a great deal of support He is not yet continent but can feed himself. He has a special chair and orthopaedic splinting to prevent drop-foot.

Remarks: These parents had accepted their child as a spastic and it came as a great shock to them when they were told abruptly that he was also mentally retarded. Their attitude to us was negative and embittered, at first, as they considered that he was much better than the other children he was placed among. They were, however relieved to find how active the physiotherapy and orthopaedic treatment was and gradually they have come to realise that their child is happier and more relaxed than ever before. The mother was subjected to a great deal of criticism from friends and relatives and tended to isolate herself. She has now a part-time job in the nursery school which the youngest child attends. The older sister has witnessed several of the patient's severe grand mal seizures and is nervous and has begun to stammer The parents, particularly the father have begun to play a very active part in the parents association. The child has numerous inter current infections and frequent epileptic seizures connected with pyrexia. The parents still overestimate the child' intelligence.

3. Boy aged 10 years with progressive muscular dystrophy and an intelligence quotient of approximately 70 He is the first of two siblings. The sister four years younger has had a nephrectomy and shows the same enzyme pattern as our patient. The father is an insurance agent and the mother has no work out side the home. The father is 35 and the mother 30. Our patient has excellent speech but is becoming progressively more handicapped and now spends most of his time in a wheel chair and has difficulty in looking after his own needs and is easily tired. He comes here for three days per week only

Remarks: Both of the parents and this boy realise that the disease is progressing. The parents are also aware that the younger sister may be similarly af fected. The mother is now pregnant again and is to have a therapeutic abortion. There has been some talk of adopting a normal child. The family economy is strained as both parents have cars, the father on account of his work and the mother because of the patient. The boy has been accomodated here so that the parents and sister could go on holiday These parents were previously overambitious and the boy attended normal school which was too exacting for him both physically and mentally The mother appears to be of limited intelligence, is reported to have been word-blind and cannot carry out any special treatment in the home The younger sister ppears normal and attends nursery school.

4. Boy aged 3½ years. He is the forth of four siblings. The father is an engineer and the mother who is Norwegian-born, has had work outside the home for a brief period. The father is 41 and the mother 32. The father appears to be mentally unbalanced and has contacted a great number of prominent people by phone on the child's behalf but has very little to say at personal interview. The child has spastic tetraplegia with frequent epilepsy and pyrexia probably of cerebral origin. Severe anaemia, probably of nutritional origin, is present. Rhesus incompatibility was present and the possibility of an inborn error is being investigated. He is completely helpless and has had repeated periods of hospitalisation: on one occasion for dialysis on account of anuria and for various orthopaedic operations.

Remarks: The mother is not accepted by her husband's family who consider that the child should be in an institution. Previously she did not dare leave the child alone but after he had commenced day care here she took a job 1½ hours daily where she was very happy. Unfortunately she has now developed disc prolapse and has had to abandon her job. The older children aged 12, 9 and 8 have long been unkempt and neglected and have now begun to play truant and steal. Our patient is filthy and neglected. The mother realises that she needs healp. Temporary inpatient treatment is being offered while she receives treatment for her back. Both parents have now agreed that inpatient treatment will become necessary when place is available.

This mother indulges in wishful thinking and assures us that the boy can walk and can answer questions. She appears to get very little real help from her husband.

5. Girl aged 10½ years and the result of a twin pregnancy. The other twin died in utero. She has healthy younger brother. This patient has spastic diplegia with athetosis, hypermetropia and convergent strabismus. Her intelligence quotient is now 43. She is able to walk indoors with the aid of a special support and orthopaedic footwear. Her speech is excellent and she is able to attend her personal needs. The father is a hospital manager and the mother trained dispenser. He is aged 37 and the mother 43.

Remarks: On account of her good speech, this child appears, at first sight, to be considerably more intelligent than she actually is. The parents have difficulty in accepting this and reproach the school and nursery school staffs here for her lack of progress. The girl appears well-adjusted here in a nursery and pre-school curriculum but she is nervous and easily distracted. Both parents have some medical knowledge. The father studied medicine for two years before turning to accountancy and the mother was a dispenser. They are ambitious and press the child to scholastic feats which she cannot manage and in all respects expect too much of her. The child has had screaming fits at home. Both parents have begun to realise that they will have to consider inpatient treatment sooner or later. The two siblings are said to quarrel a great deal.

6. Boy aged 4½ years with spastic diplegia, epilepsy and strabismus. He is completely helpless, has no speech and is unable to do anything for himself. He is the second of two siblings, his sister being 16 years. The father is a master painter aged 38 and the mother a diabetic, is 37 and has a secretarial position in the local town hall. A member of orthopaedic appliances have been provided but never used and similarly a number of operations have been proposed but refused. The child has frequent epilepsy often amounting to status epilepticus. The economic circumstances appear to be good.

Remarks: These parents appear ill-matched. The father is frequently drunk. The mother is intelligent but emotional and ineffective. She uses her diabetes as an excuse for not applying the child's splints. The child has never had vitamins and never drinks milk but is always clean and well cared-for in other respects. Boots and splints supplied two years ago have been returned unused. The mother has written to many prominent persons and obtained a number of special privileges. She realises that she neglects her husband and daughter. This marriage appears to be in immediate danger of disintegration.

Boy aged 12½ years. He is the third of three siblings, his brother is 22 and sister 19. The father is an optician aged 60 and the mother trained children nurse aged 56. The boy has athetotic tetraplegia and spends most of his time in a wheel chair. His intelligence quotient is about 53. On account of his paralysis, his speech is extremely difficult to understand. He has a great variety of chairs, beds and toilet chairs and orthopaedic boots.

Remarks: On account of his expressionless face, excessive salivation and almost unintelligible speech, this child gives the impression of being more retarded than he actually is. The mother is overprotective and definitely overestimates his intelligence. However she is able to understand his speech, possibly adding remarks of her own. The boy comes here only two days weekly but his attendance has been irregular as his mother keeps him home for trifling reasons. The boy has had inpatient treatment in various wards in various institutions and the mother has repeatedly taken him home on account of trifling disagreements

about his care. The mother has had thyrotoxicosis treated operatively and now has frequent back pain. She is little and talkative but the boy is her only subject of conversation. Husband and wife are scarcely on speaking terms, the elder son has left home and is married and the mother and daughter quarrel constantly. Our patient is dressed and treated like a baby. Temporary inpatient treatment has helped the ward staff to understand the boy's speech and on this last occasion the mother has admitted that she enjoyed the relief she obtained and it is obvious to her that the boy enjoyed his stay too. Inpatient treatment will ultimately be required here.

8. Boy aged eight years. He is the third child of three siblings but has been adopted. No information is available about his own family. He is the only child in his adoptive home. Adoption took place when the child was two months of age and the adoptive parents became divorced shortly afterwards. The adoptive mother has since trained as a medical secretary and now works in a hospital. The parent has choreoathetosis and occasional epilepsy. His intelligence quotient is under 20 and he has no speech. He can be kept clean and dry. He is hyperactive, happy and babyish. He bites and chews everything. He is able to walk and run without support but wears orthopaedic boots. Recently he has had an itching skin condition which appears to be form of contact dermatitis.

Remarks: This child requires no physiotherapy and therefore would be better off in a nursery school for more active children. On account of his constant purposeless activity he is a nuisance among and a danger to the helpless patients. The mother is intelligent but makes intrigues. She is an active representative for the parents association. She is fully aware of the child' mental state and limited abilities but uses her slight medical knowledge to demand various investigations and treatment. She knows what she is entitled to and is determined to get her rights. She stirs up conflicts among the other parents.

She rather enjoys the admiration which she receives as the adopted mother of a mentally retarded child. She has had the child with her on holidays abroad. The boy is not suitably placed in this ward but all attempted transfers have been unsuccessful.

9. Girl aged 14 years, the first of four children. She was born with a large myelomeningocele in the lumbar region which was treated operatively. She has now slight hydrocephalus, flaccid paralysis and anaesthesia, which is complete in one leg and partial in the other and a neurogenic bladder. She is able to move about with splints and crutches indoors but spends most of her time in a wheel chair. Her intelligence quotient is approximately 70. Her twin brothers aged 12½ are both backward and attend a special school. One of them has shown symptoms of maladjustment in the form of theft and school difficulties. The youngest brother aged 5 attends a nursery school for spastic children on account of ataxia of obscure origin which appeared when he started to walk at the age of nine months. His speech is poor but his intelligence quotient has risen steadily and is now 90. The father aged 39 is a goldsmith but works as a driver. The mother aged 38 is a dressmaker and the stable breadwinner of the family. She goes out as a charwoman at 4 a. m. daily. The father is frequently drunk and the home is dirty and neglected.

Remarks: Despite her handicaps, our patient is responsible for serving breakfast and getting her brothers off to school in the mornings before she comes here. The mother works hard to support this grossly abnormal family and sews clothes for our patient who is so misshapen that ready-made clothes do not fit. Our patient attends a club for young cripples but feels very sensitive about her urinary incontinence which is being investigated. At present, treatment is being concentrated on training her to be independent so that she can live in a hostel or collective house later.

10. Girl aged 11 years, the second of two sisters. The father aged 48 is a machine worker and the mother, aged 42, had a domestic job in a hospital prior to her marriage. The patient has a spastic hemiplegia on the left side and a severe speech defect. She is able to walk without support. Her intelligence quotient is approximately 48. She still needs to be reminded about her toilet needs. At present she is receiving special training of the muscles of her tongue and mouth.

Remarks: This patient is a happy little girl but her concentration is poor so that any change in routine upsets her. Her mother feels that she is much better than the other children in the ward and nursery school and neglects the four-year older sister. The patient still needs a great deal of help with her daily activities, dressing, toilet nedds, transport etc. The mother is fussy and overprotective and expects too much from the older sister who has now begun to play truant from school.

11. Girl aged 10½ years, the oldest of three sisters of whom the other two are healthy. The father is a banker aged 3_ years and the mother (also 32) worked in a tax office until her second pregnancy. The patient has hydrocephalus treated with a valve, spas-

tic quadriplegia, epilepsy myopia, and strabismus. She can walk with a special support but has been particularly timid since the last orthopaedic operation and lacks confidence She requires help with toilet. There have been no epileptic seizures for many years. Her intelligence quotient is approximately 42.

Remarks: The relationship to the younger sisters appears to be good. The patient has interests in common with her youngest sister The mother is small and is now having difficulties in carrying the patient. Various temporary stays in holiday homes have been arranged to give the mother a rest.

The mother feels that the child is not making sufficient progress. A conference has therefore been arranged with the nursery and school staffs so that both parents can be helped to understand the patient intellectual limitations.

12. Boy aged 9½ years. H is the fourth of four siblings, and has sisters aged 20, 19 and a brother aged 17 years. The father is a driving instructor aged 51 years and the mother is a trained nurse aged 45 and works at present as a relieving night sister The boy intelligence quotient is less than 20. H has spastic tetraplegia with athetosis, epilepsy and chronic constipation. H is completely helpless and has no speech. There is excessive salivation. H can move about slightly with mechanical support but his movements are purposeless.

Remarks: The mother had previously considerable help from the older sisters. These have now left home and one of them is now working with mentally retarded children. The mother realises that sooner or later inpatient treatment will be necessary Temporary inpatient stays have been arranged to enable the parents to go on holiday The father has been in mental hospital and there have been marital difficulties.

13. Girl aged 12 years, the older of two siblings. Her brother aged six years is normal. The father is mechanic aged 41 years and the mother housewife of 38 years. The girl has microcephaly spastic tetraplegia, epilepsy and severe mental retardation. She salivates profusely She has no speech but is invariably happy and smiling. She has had several orthopaedic operations in the form of tenotomies and tendon lengthening. Her intelligence quotient is less than 20. She can move about in an aimless manner with mechanical support and can slide about on the floor without support. She cannot attend to any of her own needs. The family live in house on two floors and it is now becoming difficult to get the child up and down stairs. They have a car which, however is not large enough to accomodate wheel chair The child is too retarded to attend a nursery school.

Remarks: This mother has realised for some years that it will become increasingly difficult to look after the child at home on account of her increasing size and helplessness. In short, the child is well ccepted by the family who have no illusions about her future development.

14. Girl aged 15½ years. She is the third of four siblings of whom only one the eldest sister is normal. An older brother is mildly retarded and the younger brother has spastic paresis in both lower limbs and has attended a school for physically handicapped. The father was sentenced to three years in mental hospital following incest with the elder daughter The parents were divorced in 1960. Our patient has spastic quadriplegia but retains considerable use of the left arm. She is able to mov about indoors with crutches but her balance is poor and she has occasional falls. She is myopic and wears glasses. Her physical handicap necessitates helmet, orthopaedic boots, crutches and wheel chair Her speech is excellent and belies her intelligence quotient which is only 60 The mother who is 47 works in a laundry She lives with the two youngest children in four-roomed house of which the two rooms are rented out. The patient ttends school and receives individual tuition. She can read and write and do simple handwork.

Remarks: The elder sister her husband and two small children are of considerable support to this family The older brother lives in a rented room and works in a sheltered workshop. There is considerable jealousy between our patient and her younger brother who is better endowed intellectually The mother is overprotective of our patient and very prudish (cf. incest mentioned above). The mother has periods of depression and backaches. Our patient is an odd mixtur of extreme childishness and domination and she utilizes her handicap. She has now developed typical teenage interests and the mother appears to be very afraid of her growing interest in the other sex. Our patient cannot be left at home alone as she is unable to get up from bed, is heavy and has frequent falls. She has been offered frequent periods in various holidays homes. She adjusts herself well to these changing environments and enjoy them. Training at present is being concentrated on making her as independent as possible prior to transfer to an institution for young people. It has been difficult to get the mother full co-operation.

15 Boy aged 8 years, the second of two siblings. The father master builder aged 51 years has two adult children from previous marriage. The mother also

aged 51 years is a housewife. The twelve-year-old sister is healthy. Our patient has multiple congenital defects including hydrocephalus, hypertelorism, mental retardation (intelligence quotient under 20), spastic tetraplegia most marked in the lower limbs, kyphosis, pigeon chest and congenital heart disease and is suspected to be suffering from the *Morquio Ullrich syndrome*. Recently his condition has been complicated by inguinal hernia, hydronephrosis and pyelonephritis. H has no speech but can make his needs known by gestures and noises. A toilet regime is employed but the child is not yet toilet trained. Equipped with long splints, he can stand with support but his balance is poor. H can move around on a specially constructed tricycle. He has sustained repeated concussions as the result of apparently trivial falls some of which resulted from being pushed by another child. He has, therefore been transferred to another ward with smaller and less active children.

Remarks: The parents of this child are relatively elderly. The mother is overprotective and her confidence in the hospital has been shaken after the repeated falls. This pleasant smiling little boy can dominate his sister and mother but shows respect for his father's authority. The sister has not shown any behaviour difficulties but appears to function as a far too docile little nursemaid for her brother. She does not appear to have normal childish interests and the relationship seems unhealthy. The mother is naturally afraid of losing the child and his frequent illnesses and admissions to hospital have been a continual reminder of this.

16. Boy aged 3½ years, the first of two siblings. Both parents are 4 years of age. The father is a carpenter and the mother runs a little hairdressing business in her home. The infant sister is healthy. Our patient suffers from hydrocephalus, strabismus and infantile spasms. Urinary infection has been relieved by circumcision. The child has no speech, he has to be fed, is not toilet trained and has profuse salivation. He can move about on the floor on his back with the head in hyperextention but requires support while sitting and can neither stand nor walk. His intelligence quotient is estimated to be 34. H suffers from motion sickness and frequently omits during transport.

Remarks: So far this oung family have no particular behaviour problems. The boy was admitted here as an inpatient during the birth of the infant sister and on a previous occasion while the parents moved to a larger house. H receives day-care for two da s only per week. During the second pregnancy the mother was nervous about the outcome and received sedation. Thanks to her own little business, the mother does not feel isolated.

17. Boy aged 12½ years, the second of three siblings of whom the first was stillborn. The surviving sister is one year younger than the patient and healthy. The father is a master carpenter aged 59 years who travels a great deal in connection with his work. The mother is a housewife aged 46 years. The patient suffers from spastic tetraplegia which is most severe on the right side and epilepsy. He is able to walk with no special support or appliances although his gait is hemiplegic. H has no intelligible speech, facial paresis and profuse salivation and he is not yet toilet trained. He can feed himself but cannot chew. He wears orthopaedic boots and has abduction splints which he wears while resting. No recent tests have been performed but the intelligence quotient is estimated to be about 40.

Remarks: This child is pleasant and easy to look after here but is said to tyrannize the family at home. The mother is frequently alone with the two children. She frequently complains about slight illnesses in the boy and it is seldom possible to confirm their existence here. She does not co-operate well in administration of the anti-epileptic medicine but there are no seizures at present. The sister is said to be nervous and the mother is menopausal which possibly explains her complaints and demands.

18. Girl aged 12½ years, the youngest of three children. Her brother is five years older and sister seven years older. The father is an accountant aged 45 years and the mother a housewife aged 41 years. Our patient suffers from petit mal, and spastic paraplegia with athetosis. She is completely helpless, has to be fed, is incontinent, can say a few words and understand some more. The family have recently moved to a new house and the father has altered the width of the doors, removed steps etc., for the sake of the patient and to accomodate her wheel chair and walking support. The intelligence quotient is bout 20. The patient is in early puberty and her antiepileptic medicine has required considerable adjustment recently.

Remarks: This patient's mother claims considerable experience in looking after helpless patients, having nursed both of her own parents during long illnesses. The new house has a sunk bath and the mother has developed backache with the lifting involved. The patient is frequently ery dirty particularly after weekends at home. The two siblings help in the care of the patient and the sister hopes to train as a teacher for mentally retarded children. This family appears to have accepted the psychological burden of a handicapped child but, because of her increasing size there are practical difficulties.

19. Girl aged 7 years, the second of two siblings. The brother aged four years older was said to develop slowly and cardiac disease was suspected in early life. He has no longer any cardiac symptoms and his intelligence is well above normal. The father is a bricklayer aged 36 from a very poor home. The mother aged 35 has no work outside the home but has good scholastic background and had held office jobs prior to her marriage. Our patient has spastic tetraplegia and microcephaly and is only able to move her head and eyes. The intelligence quotient is under 20. She has no speech but understands some very simple commands. She has to be fed and is completely incontinent. Dressing and undressing are becoming difficult on account of contractures of the shoulder girdle. She is unable to hold anything in her hands. She appears to enjoy the company of other children although she cannot participate actively in nursery school activities. Salivation is problem. She has long splints, a special wheel chair and walking support.

Remarks: This child cried a great deal during the first year and the mother was advised by relatives and neighbours and her husband to have her put in an institution which she steadfastly refused. The mother treats the girl like living doll and she is always beautifully cared for and dressed. The brother developed increasing behaviour difficulties some three to four years ago. These necessitated placing first in a residential school followed by admission to department for child psychiatry and he now attends school for autistic children where he is a class of three pupils and still has severe contact difficulties. Testing revealed extreme jealousy with destructive phantasies directed towards the handicapped sister. The father previously avoided all contact with hospitals but has recently begun to attend the monthly parents meetings at the boy's school where intensive attempts have been made to get both parents to help and understand the boy and his problems. The father previously escaped from the family situation by taking overtime work but is now co-operating. The mother has previously denied all difficulties but there can be no doubt that she devoted much of her time and energy to the care of the little girl at the expense of the boy. The maternal grandmother seemed to understand the boy better than anyone else and could manage him. Unfortunately she died after long illness some two years ago. These parents come from very different backgrounds but appear genuinely found of one another and seem to be making great efforts now on the boy behalf. Future inpatient treatment of the girl is being planned and short temporary inpatient stays have already been arranged to prepare the way.

It is difficult to be absolutely certain that the emotional deprivation to which this boy was exposed was the sole cause of the development of autism but it appears to have been a major contributory factor. The beautiful bibs with hand-embroidered floral designs with which the little girl is equipped are symbolic of misplaced mother-love. Salivation is a great problem and she must have dozens of bibs!

This particular case prompted the author to commence the investigation which has revealed other similar cases none of which are so striking, however.

20. Girl aged 9 years, the second of four siblings. The father, aged 34, works at the airport as a truck driver. The mother aged 3_, had previously domestic work in hospital for infectious diseases. Our patient, in addition to mental retardation with an intelligence quotient of 44, has severe reduction of hearing and consequent reduction of active speech and is atactic with right-sided hemiparesis. She is able to walk for short distances outside with elbow crutches and orthopaedic boots which hav to be re-soled once a fortnight. Indoors she can walk with support of furniture. She uses hearing aid and receives special tuition in speech and lip-reading. Her active speech is still difficult to understand. She is helpful with the other patients and can attend to her own needs. The family has recently moved from small flat to terrace house with garden. They have a car. The patient previously came here on only three days per week but now comes five days weekly and is making excellent progress.

Remarks: The rent in the new house is really more than this family can afford but they appreciate the house and the freedom it gives them. Previously when they lived in flat, our patient's noisy play disturbed the neighbours. The family finances are somewhat strained. This family is quite the most normal in the material as regards their acceptance of the child and her handicap. Perhaps her deafness could have been detected at an earlier age if they had been more alert. They realised early that the child's development was slow. The The patient plays well with her younger sister and brother aged 3½ and 1½ years respectively. She shares their interests but on account of her size she adopts maternal role both at home and in the nursery school. Despite their strained economy the parents do not complain and are very grateful for everything that is done for them. Recently they were persuaded to accept quantity of bedclothes from a boarding school which was closing down which must have helped their situation considerably. The older sister is normal and doing well at school.

Comments and discussion

The material investigated here is too limited to permit the drawing of far-reaching conclusions. It can only be regarded as an illustrative sample. It confirms, however, impressions gained from outpatient and inpatient clienteles that *the siblings of multihandicapped children living in their homes are frequently subjected to very gross neglect*. This is seldom deliberate but is due solely to the overpowering needs of the handicapped child. Both parents may also suffer from the strains involved and marriages are frequently threatened. The author has seen several cases within the past year where permanent inpatient treatment of the handicapped child has relieved the situation, not only for the overworked and exhausted mother but where the well-being of the entire family was concerned. Similar findings are quoted from England, Australia and USA from an unpublished paper by Holt in the Appendix of the leaflet "*Stress in families with a mentally handicapped child*" (19). The present paper concerns mentally retarded children who have simultaneously motor handicaps so that the burden is twofold.

From the summarized case histories and the Table, it will be obvious that practically all of these children require some special forms of equipment in their daily care. This varies from glasses, helmets, various forms of orthopaedic splints for day or night use, footwear, wheel chairs and walking supports. The correct employment of these devices involves skill and training and provides extra work and responsibility for the parents. Many parents, in fact, do not use the splints and medicine prescribed so that treatment is sabotaged. More than half of the patients are incontinent and, in some cases, excessive salivation presents almost as great a problem. With their increasing size, the helpless patients present increasing physical burdens for the parents who are now past their prime. Many of the mothers are alone although only two are divorced (Cases 8 and 14). In other cases, the father appears to take very little active part in the care of the child for reasons such as overtime work, work involving travelling, drunkenness and ill health (Cases 1, 6, 7, 9 and 19).

The occupations of the parents are recorded to give an impression of the social status. This revealed another interesting point, viz. that a considerable number of the mothers had been employed in some form of paramedical occupation (e.g. domestic work in a hospital) prior to the birth of the child concerned (Cases 5, 7, 10, 12 and 20). This may be of etiological significance e.g. exposure to infection, radiation or intoxication during pregnancy. This is an incidental finding and outside the scope of the present article. Such a background must definitely be an asset for the mother of a handicapped child. Other mothers have taken up some form of work in hospitals or with handicapped children after the birth of their retarded child (Cases 2 and 8).

What is the fate of the normally endowed siblings from these homes? This investigation was prompted by Case 19 where the mother's complete absorption in the care of the microcephalic girl appears to have been the main predisposing factor for the development of autism in the older brother. Seen from his point of view, he was ousted from his position as only child at the age of four by a sick baby who screamed almost continuously for the first year of her life and who has made little progress in seven years. The maternal grandmother had apparently sufficient intuitive insight to alleviate the situation and was able to provide the boy with some of the affection and attention of which he was otherwise deprived. She has since died. Until recently the father appeared to be incapable of providing the comradeship which the boy needs. The school for autistic children which he attends holds parents meetings every month but usually only the mother attended. Recently she

was prevented from going by illness and the father attended for the first time. The school staff are working hard to help the parents to understand the situation and temporary inpatient treatment for the handicapped girl is being arranged by way of preparation for permanent inpatient treatment at a later date

In some cases (1, 6 7 and 19) the impression is gained that the mother escapes from other problems (i. e those of her husband and normal children) by devoting herself to the care of the handicapped child to the exclusion of everything else, viz a sort of oversimplification of the problem. In other families (1 10, 12, 13, 15 and 18) the normal children are expected to participate in the care of the handicapped child. This, in itself, is not unreasonable, particularly where there are several normal children who can share burden. In some cases, however for example Case 15, a slightly older sister functions as a "little mother for the sick boy The boy in his turn, tyrannizes her This little girl appears far too old for her age, and in short, appears to have been deprived of part of her childhood. In this and similar cases, it would be in the interests of the healthy child or children to provide full-time inpatient treatment for the handicapped child. In other families, the mother is simply so stressed and overworked that the other children are left to fend for themselves and this has resulted in behaviour difficulties, truancy and shoplifting (Cases 4, 9 and 10).

Make-believe is an apparently harmless pastime in which some of the parents indulge. It is in *A Day in the Death of Joe Egg* (20) where the parents of a spastic, epileptic and severely retarded child indulge in repartee each quoting to one another remarks they pretend the child has made. The extent of the make-believe varies from slight overestimation of the child's abilities to something almost amounting to mythomania. In this series, it is present to some extent in cases 1 4, 5, and 19. Case 1, (see photograph) a completely helpless boy of ten years with contractures and primitive reflexes, is said to be able to discriminate between various forms of classical music, know his way about in town and know where various friends of the family live and to have his own favourites among these The mother of Case 4 reports that the child can walk and reply to questions with affirmatives or negatives but followed this statement with there mark I know you don t belive me, but it is true!" The ambitious mother of Case 5 a girl of 10" who is receiving pre-school training, appropriate for her I. Q of 43, asked if she could tell people that the child was now in the second grade, indicating wishful thinking Case 19 is a microcephalic child of seven years who is almost rigid with spasticity Her only voluntary movements are of her eyes and head. At home, she is said to play football and to bake cakes for us every Christmas. The mother trains her every evening despite the fact that she receives adequate daily physiotherapy here and is tired in the evenings. Attitudes such as these make it very difficult to assess and progress as this in itself is bound to be slight. What is the use of helping the child to gain head control when the parents already state that she can play football! A slighter element of make-believe is present in a number of other cases and is expressed by the fact that the parents consider their child to be better than the classmates or they reproach the teaching staff because academic progress is slow

The fact that siblings have learnt in their homes something of the care required by a handicapped child does not invariably have negative sequelae. Several of the older siblings have chosen careers which involve the care of handicapped children in one form or another (Cases 1 (where two sisters are now working with handicapped children) 12 and 18) The mother of one of the children (Case 12) works as a night sister in a hospital for children and another mother helps in a nursery school and would like to train as a nursery school teacher for retarded children (Case 2)

Some mothers suffer from the misapprehen-

sion that they are the only person in the world capable of looking after the sick child. (Cases 1 7 19) They appear to enjoy a sort of martyr role" and bitterly resent the discovery that other people can, and do, care for the child as efficiently as or even better than they had done themselves. It is understandable that these mothers, who have perhaps cared for the child alone for many years with a minimum of help have great difficulty in letting others take over the responsibility and may be very critical. Many of these have been offered in-patient care of the child on repeated occasions but have consistently refused (Cases 1 6 7 and 19) They may have imagined that the child was doomed to a very short life and have determined that this should be as happy as possible. Case 6 is a striking example. The mother who is well above average intelligence, keeps the child beautifully clean and dressed but she has never given him vitamins or milk and has refused all corrective orthopaedic appliances and operations She complained of the inconvenience caused by the child's epilepsy but when revision of his medication was suggested she averted that the seizures did not worry him! In actual fact, he has had threatening status epilepticus on several occasions. The mother of Case 1 shows similar traits. Her child has severe postural defects which corrective splinting could have corrected, a mouth full of rotten teeth, a purulent middle ear infection with an ulcer on the pinna which is suspected of being malignant. She resents the fact that ailments are now being treated and insists on supervising all treatment. Her indignation reached a crisis when a biopsy was performed on the ulcer and, despite all explanations, she is still uncooperative. Another explanation in these two and similar cases may be that the mother unconsciously wishes that the child were dead and has therefore, refrained from treating these intercurrent conditions in the (unconscious) hope that they may prove fatal.

Other mothers have isolated themselves from their surroudings by the abnormal life they are forced to live (Cases 2, 4 7 and 19) Where a mother is either able to have a job outside the home or has other interests, the situation is far better for all concerned.

The handicapped child presents some of the same problems as a new baby but does not progress so very far from the baby stage so that the siblings and parents seldom see much progress. The child increases in size so that pure physical strength is necessary in the care In some cases in this series, the disproportion in size between tall very helpless, spastic children and tiny middle-aged, mothers is extremely striking (Cases 7 11 13) It is not surprising therefore, that backache can become a dominating problem in these mothers. (4 7 17 18)

Care of the child can be time-consuming. Feeding is slow and laborious Special day and/or night splints, chairs beds and other gadgets are frequently necessary Small homes can be filled with devices for the use of the sick child, including walking aids prams, wheelchairs so that little room is left for the possessions of the normal children.

Many of the children have epilepsy and its treatment adds to the responsibilities which have to be shouldered by these parents. The older sister of Case 2, a girl aged 8 years, has witnessed several grand mal seizures and these have been a terrifying experience for her She is now very nervous and has a tendency to stammer

An attempt was made to see whether there was any correlation between the basic mood of the handicapped child and the mental attitude of the parents, particularly that of the mother Only one child, Case 1 can be described as being unhappy He cries a great deal, possibly on account of painful muscle spasms or pain from the ulcer on his ear His mother is tired and depressed. The remainder of the children are described as having neutral or happy basic moods. Only three of ten happy children appear to share their happiness with their parents (Cases 13, 18 and 20) The staff

here cannot help being infected with the carefree happy-go-lucky moods of these children and the explanation of demanding, critical querulous natures of some of the parents remains somewhat of a mystery The parents of Case 3, the boy with progressive muscular dystrophy have a very natural cause for their anxiety Perhaps it would be more correct to describe the happy mood as pathological, almost amounting to euphoria, comparable to that encountered in disseminated sclerosis. It certainly is a very primitive form of happiness but is a feature which makes work with these children rewarding The remaining children are described as having neutral basic moods. Their parents, in contrast to the parents of the happy children appear to be more normal.

Poverty as such, does not appear to affect the health or happiness of the siblings in this material. Case 20 belongs to quite the poorest family in this material. Nevertheless, this family seems to be mentally quite healthiest and best balanced. In contrast, many of the handicapped children of families from high social levels appear to be grossly neglected in contrast to the family situation as a whole (Cases 4, 18)

In three families other siblings are also handicapped (Cases 9 14 and 19) In family 9 all four children appear to be educationally subnormal. Our patient had a large myelomeningocele, slight hydrocephalus and slight mental retardation. Twin brothers aged 12½ are both educationally subnormal and have school difficulties despite special school facilities and the youngest brother suffers from hyperactivity and ataxia with considerable retardation of speech. This raises the suspicion of a common etiological factor In family 14, three out of the four children are handicapped and the father was admitted to a mental hospital after incest. The oldest daughter is normal, married and has two normal children and she and her susband are of considerable help in the normalization of this family The second child, now a young man, is backward, has worked in a sheltered workshop and is now independent. Our patient has a severe spastic triplegia and slight mental retardation and the fourth child is also spastic but intelligent enough to attend a normal school. Here also, a common etiological factor appears to be involved. Family 19 has been mentioned already Our patient is a girl with severe microcephaly she is spastic and with a very low intelligence quotient. Her older brother was apparently normal in infancy and early childhood but developed austitic tendencies at the age of seven years and, at 11½, is still attending a special school for autistic children. The presence of the multihandicapped sister appears to have been a factor of considerable etiological importance in the development of his autism.

The fathers of Cases 4, 12 and 14 have had treatment in mental hospitals but further details are not known. Two fathers drink excessively Mental breakdown requiring hospital treatment does not appear to be present in any of the mothers.

The prospects for normal siblings seem to be worst in families in which there are only two siblings or when the other siblings are of much the same age as the handicapped child. The normal child must then compete with the handicapped child for parental affection and attention. If the handicapped child requires much care, then even parents with robust physical and mental health will have difficulty in fulfilling their obligations to both children. This is particularly the case when the normal child is a few years senior to the handicapped sibling and parents and relatives therefore expect him to understand the situation which he is unable to do because he is still a child himself Where there are several siblings who are considerably older than the handicapped child, they are more capable of helping They have had their normal childhood and can relieve the parents, as babysitters, by fetching and carrying etc. The mere fact that there are several normal children provides preponderance of normality and makes the climate in the home healthier

Table II. Schematic presentation of brief description of parents, their marriages and the siblings of the 20 children receiving day care. Siblings not mentioned individually are presumed to be normal.

Number	Father: Age	Description of Father	Mother: Age	Description of Mother	Stability of Marriage	Siblings: Over years	Siblings: Under 3 years
1	53	Poor health	53	Depressed, tired	Good	2 sisters work with handicapped children	—
2.	32	Robust, active	26	Nervous, intelligent	Good	—	Sister nervous, stammers
3.	35	Normal	30	Word-blind, rather helpless	Good	—	Sister nephrectomy abn. enzymes
4.	41	Paranoid. Has had hospital treatment	32	Disc prolapse drinks?	Constant quarrels	—	Behaviour difficulties in all 3
5.	37	Normal	4[illegible]	Anxious, ambitious	Good	—	Brother normal
6.	38	Alcoholic	37	Diabetes, demanding	Unstable	Older sister neglected	—
7	00	Disinterested	58	Backache overprotective	Unstable	Sister quarrels with mother	—
8	40	Unknown	39	Intelligent, demanding	Divorced	No siblings in adoptive family	—
9.	39	Alcoholic	36	Exhausted	Unstable	—	All 3 subnormal, behaviour difficulties in one
10	48	Normal	42	Demanding, fussy	Good	Sister plays truant	—
11	31	Normal	33	Normal	Good	—	Normal
12.	51	Has been in State Hosp.	45	Normal, nursing sister	Unstable	Sister works with handicapped children	—
13.	41	Normal	38	Normal	Good	—	Brother normal
14.	65	Invest. State Hospital	47	Nervous, depressed	Divorced	Sister normal. One brother subnormal	Younger brother spastic
15	51	Normal	51	Overprotective, nervous	Good	–	Dutiful little nurse
16.	24	Normal	24	Normal	Good	—	Normal infant
17	59	Normal, often away	40	Overprotective	Good	—	Sister nervous
18.	45	Normal, helpful	41	Backache	Good	Sister works with handicapped children. Brother normal	—
19	38	Lacks insight	35	Neurotic unrealistic	Good	—	Brother autistic
20.	34	Robust	32	Normal	Good	—	No problems

The main object of this article is, therefore, a plea for the normal siblings of multihandicapped children. They have also a right to live! The affection and attention of the parents is also their birthright! For their sakes and for the sake of the family as a whole it may often be necessary to provide temporary or permanent inpatient care for the abnormal child

The 20 handicapped children in this material have all been helped. They are away from home in day care during school hours. In this respect, their conditions have been normalized but many of them have such low intelligence quotients that this form of normalization is of no significance for them. The parents are relieved of much lifting and carrying and active treatment of the children during the day The children, in their turn are stimulated by ward, nursery school or school activities suitably graded for their handicaps and they enjoy the comradeship of similarly situated children. All of the families receive allowances to defray the cost of extra laundry wear and tear of clothes etc. All orthopaedic appliances are supplied free of charge and suitable beds prams etc. can be borrowed as required. Many of families have obtained cars free of purchase tax to enable them transport the child at other times.

The children are returned to their homes, however at about the same time as the normal siblings come home from school so that these normal children still do not have the parents to themselves although the parents are less exhausted than they would otherwise have been had the handicapped children been at home all day

Numerical Assessment of Results:

An attempt has been made to present these in tabular form. Table I indicates briefly the extent and degree of the handicaps in the 20 children concerned. The various colums speak for themselves.

Table II is a tabular attempt to assess the family situation as a whole

From the facts in the tables and the case histories the following numerical results can be deduced.

Fathers Three fathers had been in mental hospitals (15 per cent)
Two fathers are addicted to alcohol (ten per cent)
One father is in failing health (five per cent)
Two fathers were divorced and had no connection with their families (ten per cent)
Three other fathers play very little active part in the family situation for other reasons such as lack of interest or pressure of work (15 per cent).

Mothers Only five mothers are described as normal (25 per cent)
Four mothers have backache (20 per cent)
One mother is possibly alcoholic and is receiving psychiatric treatment (five per cent)
One mother has diabetes (five per cent)
The majority of the mothers are described as depressed and tired, or as nervous and over protective. This group amounts to ten mothers or 50 per cent.

Marriages. There are only two actual divorces in the material (ten per cent) but five other marriages are unstable (25 per cent) Thus, 35 per cent of the marriages are not harmonious with the inevitable repercussions on home life.

Siblings The 20 children in this material have 36 siblings. (Case 8 was adopted in infancy and, though he is the third of three siblings, he is the only child in the adoptive family) In Table II, these siblings have been divided into two groups, those over the age of 15 years and those younger than this. Fifteen years was chosen as this is the official maximum age for this hospital. The siblings in the first group are, on the whole, considerably older than the handicapped child while those in the second group are round about the same age.

Among the 13 older siblings, four girls have chosen careers involving work with mentally handicapped children (30 per cent) Two of

the younger girls in this group showed behaviour difficulties (fifteen per cent) One boy is slightly retarded but able to earn his living (7 7 per cent)

Among the 23 younger siblings, six (four girls and two boys) exhibit behaviour difficulties (25 per cent) and one boy is autistic (four per cent) Thus, a total of 29 per cent of children of about the same age as the handicapped sibling have psychiatric problems which appear to be directly or indirectly related to the presence of the handicapped child in the family

Three children are slightly retarded but able to attend schools or nursery schools (13 per cent). Their presence suggests an etiolog ical agent which must have pre-existed the present situation.

Siblings not mentioned individually in the Table are presumed to be normal.

Ideally schools nursery schools and general practitioners should have been contacted concerning all of the siblings. These figures must, therefore be regarded as minimum figures.

The child who appears to the author to be most at risk is the 12 year-old sister of Case 19 As yet, she has not exhibited behaviour difficulties of any kind and she must thus still be classified as normal. She appears, however to be too good to be true and one wonders how long this will last

No control material is available but these figures appear to be in excess of those anticipated in a random section of the child population.

Proposals

Families such as those described here need help However it will be observed from the case histories quoted, that even in the cases where the need is greatest, offers of help may be stubbornly rejected until the parents are exhausted and embittered and the siblings neglected.

In an investigation of the parents of mongol babies who were admitted to childrens homes, *Inge Lise Jensen* (16) found that these parents needed great support even when they did not have the handicapped child to care for *Lee G Miller* (18) in 1968 quotes *Olshansky* (1962) who likens the presence of a mentally handicapped child in the family to a state of chronic sorrow and *Miller* subdivides the processes in adjustment in the parents into three stages I Shock and inability to face reality II Readjustment in which they partly accept and partly deny the retardation and III Reintegration in which, after a variable period of time, the parents begin to function more effectively and more realistically and also appraise the needs of the normal children. *Miller* adds however that "this stage is more often a goal than an es tablished reality Most of the families described here are in Stage II

Much time-consuming work is involved in advising these parents and, as stressed by *Howells* in 1963 (15) many factors interact. the dimensions of the family the influences of the past on the various members, the material circumstances, group characteristics and community interaction. These families must, therefore, be treated as dynamic entities.

More time and personnel must therefore, be devoted to the problems occasioned by these multihandicapped children. The parents need very sympathetic and understanding treatment if they are to continue to care for the handicapped child in their homes and probably also even if the child is given institutional treatment. *Miller* states that counselling of the parents is perhaps one of the most neglected areas in the field of mental retardation today

Where the children with the lowest intelligence quotients are concerned, the author is convinced that permanent inpatient care would undoubtedly be the best solution, if sufficient beds were available. The burden these children present to the parents is both physical and psychological so that both the physical and psychological resources of the parents become depleted and ultimately exhausted. If permanent inpatient care cannot be arranged, periodic inpatient care to enable the entire family to have well-deserved holidays is a substitute and a day and-night hospital arrangement might present a welcome solution. Both these partial solutions would also serve the purpose of gradually accustoming both the patient and the family to the arrangement. If this could be practised while the child is still small, and the physical problems involved are, similarly still small, the way would be paved for permanent inpatient treatment at a later date which would also give time for planning of the institutions required.

In allotting institutional placements not only the needs of the handicapped child and his parents but the welfare of the existing siblings and those as yet unborn must be taken into consideration.

To many these proposals with emphasis on institutional treatment may appear as an admission of defeat. If homes were larger if mothers and even grandmothers did not go out to work, if life was less stressed and hectic, then the ideal solution might be to keep these children in their own homes. In primitive societies, such conditions still exist but, at the same time, perinatal mortalities are high and infections in early childhood still flourish so that handicapped children do not have such great chances of prolonged survival. Modern civilization has brought with it both advantages and disadvantages.

The author has observed several cases within the past year where multihandicapped children were admitted for permanent inpatient care almost as emergencies on account of acute family crises. Following a period of adjustment which may be very difficult for the mother this has proved very successful in every case. The parents can and do visit their children and can be relaxed and happy without worrying about the accumulating laundry or how the neighbours will react to the noise. One mother declares that she feels ten years younger and her husband and elder daughter who had left home, have returned and a happy family unit has been re-established.

To people engaged in the treatment and training of multihandicapped and retarded children, this article contains nothing new but an attempt has been made to see the problems from another angle, viz not that of the handicapped child but that of the originally healthy members of the family It is tragic when a multihandicapped child is born but *it is even more tragic when a healthy sibling becomes mentally ill because of the parental neglect involved* (although this is seldom deliberate) It is tragic when *a healthy vigorous mother gradually becomes a tired, embittered, middleaged martyr because of the demands of the sick child.* It is tragic when *parents quarrel marriages disintegrate and fathers and older siblings leave home because of the sick child.* These tragedies are not inevitable. It should be possible, by means of advice and education of the parents and, when the time comes, by provision of suitable institutional treatment for the sick child, to prevent these tragedies.

Acknowledgements

The author welcomes this opportunity of expressing her gratitude to the various members of the staff of the Children's Hospital in Vangede, particularly Dr Jørgen Lenstrup, physician-in-charge, Erik Wamberg M. D for encouragement and criticism, Mrs Lis Broberg, psychiatric social worker for help in collection of information and the late Mrs Jean Møller Petersen for untiring secretarial assistance.

References

1. Bank-Mikkelsen, N. E.: Children's Hospital in Vangede. SA news, vol. 6, No. 1. 1968.
2. Buck, Pearl S.: The child who never grew. Training School at Vineland. New Jersey 1950.
3. Buck, Pearl S.: The good earth. The John Day Company. New York 1931.
4. Buck, Pearl S.: The time is noon. The John Day Company. New York 1967.
5. Dickens, Charles: A Christmas Carol. Chapman & Hall. London 1843.
6. Danish National Service for the Mentally Retarded: General Survey and Brief History of the development of Service Systems in Denmark. Society and Home for Cripples in Copenhagen. 1969.
7. Engbæk, Signe: Ugskr. Læg. Risk Children 1966 129:29–31
8. Engbæk, Signe: Ugskr. Læg. Risk Children 1967 129:1328–1331
9. Engbæk, Signe: Ugskr. Læg. Risk Children 1969 131:1947–195..
10. Engbæk, Signe: Ugskr. Læg. Risk Children 1970: 132:57–67
11. Engbæk, Signe: Ugskr. Læg. Risk Children 1970: 13.. 459–467
12. Friis, Birthe Elisabeth & O. Scheel Thomsen. Preliminary results of a follow-up investigation of a group of mentally retarded criminals. Ugskr. Læg. 1970:132:751–755
13. Fowle, Carolyn M.: The Effect of the Severely Mentally Retarded Child on his Family. Am. Journ. Ment. Defic. 1968 73 468–473.
14. Halskov, Therese: En undersøgelse over kontakten mellem børn på Børnehospitalet i Vangede og deres forældre. Published privately. Copenhagen. 1968.
15. Howells, John G.: Family Psychiatry. Oliver and Boyd. Edinburgh. 1963.
16. Jensen, Inge Lise: Personal communication. 1970.
17. Koski, Maija Liisa. The Coping Processes in Childhood Diabetes. Acta Pæd. Scand. Supplement. 198. 1969.
18. Miller, Lee C.: Toward a greater understanding of the parents of the mentally retarded child. Journal of Pediatrics, St. Louis. 1968 73.699–705.
19. National Society for Mentally Handicapped Children: Stress in families with a mentally handicapped child. A report of a working party. The Millbrook Press Ltd., Southampton. 1967.
20. Nichols, Peter: A day in the death of Joe Egg. Faber and Faber 1967.
21. Slaughter, Stella Stillson: The Mentally Retarded Child and his Parents. New York, 1960.
22. Tizard, J. & J. C. Grad: The mentally Handicapped and their Families. Oxford University Press. 1961.

Key words: Multihandicapped children, family dynamics, stress, mental and physical break down.

Authors address: Dr Sheila Berggreen, Strandvejen 215, 2960 Rungsted Kyst, Denmark.

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics, Lisbon, 1962.* Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Heiss, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic study. Sw. kr. 30.— 1964
155. Engström, Ingemar, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr. 25.— 1964
157. Brante, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type 1 (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress.* Stockholm, 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Pohjavuori, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Landmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Diseases during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glasser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., …ectasis: A Review of 187 Cases in Children with Follow… Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
…, Anne-Lise, A Prognostic Study of Juvenile Rheuma… Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966
…Torben, Leukaemia in Infancy and Childhood. A Mate… Danish Cases. Sw. kr. 30.— 1966
… Focal Spike Discharges in Children. Longitudi… Sw. kr. 25.— 1966
… Intracardiac Phonocardiography of the Right Heart … Sw. kr. 30.— 1966
…, Margot, Studies on Encopresis. Sw. kr. 30.— 1966
…, Lars, Bacterial Infection in Cases of Perinatal Death. A …orphological and bacteriological study based on 264 autopsies. … kr. 20.— 1966
…schrift in Memory of Constantin Chervais. Sw. kr. 35.— 1967
…, B. Zoe, The Esophageal Electrocardiogram during the …st Week of Life. Sw. kr. 15.— 1967
…, Per Owe, Atrial Septal Defect of Secundum type. A …nical study before and after operation with special reference … haemodynamic function. Sw. kr. 25.— 1967
…, Pascal, Vectorcardiographic Studies in Newborn In…nts. Sw. kr. 25.— 1967
…, Bo, Studies on Respiratory Syncytial Virus Infection. … kr. 20.— 1967
…Proceedings of the Fifteenth Northern Pediatric Congress. Bergen. …67. Sw. kr. 35.— 1967
…, Brian, Echoencephalography in Paediatric Practice with …pecial Regard to Measurement of the Ventricular Size. Sw. … 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Olof Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The Intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Elin, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1968
188. Meeuwisse, Gunnar W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Ilbrahad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Kaiblinen, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vahlne, Lorens, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kuusisto, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thern, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969
197. Sands, Ruvn, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Villaniemi, Ekke, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Soule, Dina M., Cravioto, Joaquin, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette K., Hartman, Phyllis, Bator, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer, L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 35.— 1970
210. Rosberg, Georg, Parental Attitudes to Pediatric Hospital Admissions. Sw. kr. 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Hultborn, Alps, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Lundmann, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971
214. Samuelson, Gösta, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 25.— 1971
215. Bergqvist, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr. 25.— 1971

Price Swed. kr 25.—

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB Uppsala

720071

ACTA PÆDIATRICA SCANDINAVICA SUPPLEMENT 217 1971

PEDIATRIC WORK PHYSIOLOGY

PROCEEDINGS OF THE
KAROLINSKA INSTITUTET SYMPOSIA
HOLD IN AUGUST 30 – SEPTEMBER 1 1970
S T GÖRAN'S CHILDREN'S HOSPITAL,
STOCKHOLM, SWEDEN

EDITED BY CLAES THORÉN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDE

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 217 1971

PEDIATRIC WORK PHYSIOLOGY

Proceedings of the
Karolinska Institutet Symposia
hold in August 30 — September 1 1970
S t Goran s Children s Hospital Stockholm Sweden



Edited by
CLAES THORÉN

STOCKHOLM 1971

These supplement was published
by genorous economical support
by The Swedish Diabetes Association

PEDIATRIC WORK PHYSIOLOGY
CONTENTS

Foreword 5
P Karlberg

Introduction 7
C Thorén

I

METHODS OF ERGOMETRY IN CHILDREN

Key-note Definitions, Testing Procedures, Accuracy and Reproducibility 9
P-O Åstrand

Determination of W 170 and Maximal Oxygen Uptake in Children by Different Methods 13
R Mocellin H Lindemann J Rutenfranz & W Sbresny

Direct and Indirect Estimation of Maximal Oxygen Uptake in Pre-pubertal Boys 18
L Hermansen & S Oseid

Comparison of Continuous and Intermittent Tests for Determining Maximal Oxygen Intake in Children 24
J S Skinner O Bar-Or V Bergsteinová, C W Bell, D Royer & E R Buskirk

Intermittent Exercise of Supermaximal Intensity in Children 29
M. Máček J Vávra & B Mrzena

Treadmill Exertion in Children Aged Five 32
F Klimt

Investigations on the Standardization of Ergometry in Children 35
F Klimt & G B Voigt

Physical Fitness of the Czechoslovak 12 and 15 Year-Old Population 37
I Seliger V Cermak P Handzo, J Horak Z Jirka, M Máček M Pribil J Rous, O Skranc J Ulbrich & J Urbanek

Exercise with Concentric and Eccentric Muscle Contractions 42
H G Knuttgen F B. Petersen & M Klausen

Exercise Studies in Children Using the Indirect (CO_2) Fick Method 47
C.T M Davies & S Godfrey

Cardiac Output Determination in Exercising Children—Methodology and Feasibility 49
O Bar-Or & R J Shephard

Cardiac Output During Exercise in Pubertal Boys 53
B O Eriksson

II

CLINICAL ASPECTS OF PHYSICAL TRAINING IN CHILDREN

Key-note Ergometry and Physical Training in Pediatrics with Special Reference to Pulmonary Function 56
J Bjure

Physical Training in Normal Boys in Adolescence 60
B Ekblom

The Influence of Age and Sports Training in Swimming on Physical Fitness 63
V Sobolová, V Seliger D Grussová, J Machovcová & V Zelenka

A Physiological Analysis of Former Girl Swimmers 68
B O Eriksson I Engström P Karlberg B. Saltin & C. Thorén

Preliminary Report on the Development of Lung Volumes in Young Girl Swimmers 73
I Engström B O Eriksson P Karlberg, B Saltin & C. Thorén

Investigations of the Physical Working Capacity of Obese Children 77
R. Mocellin & J Rutenfranz

Body Composition and Fitness in Obese Children and After Special Treatment 80
J Parizkova, M Vaneckova S Sprynarova & M. Vamberova

Circulatory and Respiratory Dimensions and Functional Capacity in Boys Aged 8—13 Years with Bronchial Asthma 86
S. Bengtsson B O Eriksson I Graff-Lonnevig S Kraepelien & B. Saltin

Intensive Physical Training in Children with Bronchial Asthma 90
J Vavra, M. Macek B Mrzena & I Spicak

Working Capacity and Physical Training in Asthmatic Children at 1800 m. Altitude 93
F Geubelle C. Ernould & M Jovanovic

Quality and Significance of Pulmonary Adaptations to Work in Adolescent Altitude Residents 99
J A. Dempsey

Effect of Physical Training on Central and Peripheral Circulation in Adolescents with Motor Handicaps 105
A Lundberg

Remarks on Physical Training of Children with Cerebral Palsy 106
K Berg

Maximal Aerobic Capacity of 6—15 Year-Old Girls and Boys with Subnormal Intelligence Quotients 108
O Bar-Or J S Skinner V Bergsteinova, C. Shearburn D Royer W Bell J Haas & E. R. Buskirk

Physical Capacities of Mentally Retarded Children 114
F W Katch & S A Zaretsky

Physical Capacity and Training in a Group of Young Adult Mentally Retarded Persons 119
B Nordgren

Correlations between Muscular Strength and Industrial Work Performance in Mentally Retarded Persons 122
B Nordgren & L. Bäckström

III

MUSCULAR METABOLISM DURING EXERCISE

Key-note Muscular Metabolism and Physical Exercise 127
G Haralambie

Physical Activity by Adolescents 133
J V G A Durnin

Body Composition in Children A Reference Standard for Maximum Aerobic Power Output on a Stationary Bicycle Ergometer 136
C. T M. Davies

Short time Exercise and Nutritional Status in Ethiopian Boys and Young Males 138
N H Areskog

The Effects of Repeated Prolonged Exercise on Plasma Hormone, Insulin, Glucose, Free Fatty Acids, Glycerol, Lactate and β-Hydroxybutyric Acid in 13-Year Old Boys and in Adults 142
B O Eriksson B. Persson & J I. Thorell

Hormonal and Metabolic Changes During and After Prolonged Muscular Work in Prepubertal Boys 147
S Oseid & L. Hermansen

Muscle Metabolites During Exercise in Pubertal Boys 154
B. O Eriksson J Karlsson & B. Saltin

FOREWORD

The subject of the symposium is of great interest and significance, ranging from human biology to social development.

Human being uses 1/3—1/4 of his life in growth and development in preparation for the rest, and so also in working performance.

In terms of the maximal absolute level the gradual increase levels off in late adolescence. Thereafter a decline starts, slowly in the beginning

The subject deals with dynamic phenomenon with interwoven interrelated factors from conception to the grave during biological aging· development of functional dimensions and maximal functional capacity the changes in basic functional demand and changes in patterns of physical activity with age, i.e. the normal physical training

There are, however great variations in individual *physical training· influenced by a great* number of disorders of different operating mechanisms and by superimposed exogenous training factors.

The main question is how to achieve optimal functional development for each individual in relation to his primary circumstances, with the elimination, compensation or decreased influence of disturbing factors.

The symposium is well balanced between methodology clinical aspects and muscle metabolism, i. e the mechanism of the basic working motors.

As a pediatrician with a special interest in growth and development and clinical physiology it is a great honour and pleasure for me to wish you a fruitful meeting The possibilities seem to me extremely promising with such a group of participating research-workers in the fields who have decided to spend three days in discussion the subject.

On behalf of professor Rolf Zetterström, who unfortunately was not able to be here today I wish *you most welcome to this Third International Sym*posium of Pediatric Work Physiology

Petter Karlberg
Professor in Pediatrics
University of Göteborg, Sweden

INTRODUCTION

During the past decade work physiology has given us increased knowledge about the complexity of physiological functions during muscular work of different kinds. The regulation of central and peripheral circulation during exercise, as well as many other functional changes in individuales of different ages, sex and with different degree of training, has ben thoroughly studied but to a very limit extent in children. In the recent years muscular metabolism during exercise has also come to be more clearly understood. In another symposium held in Stockholm in 1970 knowledge in this field was presented and published in *Muscle Metabolism During Exercise* (Ed. B Pernow and B. Saltin, Plenum Press, 1971)

Physical activity and training have gained increasing acceptance as being important to adults health in developed and urbanized societies. Physical training is today also recommended as rehabilitation therapy after different diseases or handicaps. Prophylactic physical training to counteract unhealthy inactivity changes and coronary heart disease has become an important part of modern physiotherapy. For pediatric ages, many factors are involved, which mak ergometry and other physiological examinations more difficult to nterpret and evaluate. Thus, body size, individual growth increase, degree of maturity and functional training must be taken nto consideration. Body composition and temperature regulation are other factors which differ from adults age groups.

The development of different functional dimensions such as heart and lung volumes, total hemoglobin and of physical fitness during growth are of pediatric importance. The influence of physical training on this somatic development has become better elucidated through the intensive physical training, which in some cases starts long before puberty Work physiology has also shown that there are special problems in lower age groups and during puberty and that methods must be suited to the child. The examination must often use play as motivation, especially in the pre-school ages. In school ages, competitions or other motivating attractions can be necessary to obtain the child's complete co-operation. Existing fear of blood samples and anything that can hurt demands patience, a knowledge of children and a good hand with children so that the examination will be less stressing emotionally This should be required of the whole staff of a physiological laboratory working with children. The ethical roles for clinical research must be considered, and parents need good information about the examination. In the Recommendations of the World Medical Association (Declaration of Helsinki 1964) the basic principles for clinical research on a human being demand a free consent after information. This means in pediatrics that the parents also had to give their informed consent.

I recent years much work on pediatric work physiology has been done in an increasing number of laboratories and important progress in this field has been made. It has therefore become logically

necessary for physiologists and pediatricians interested in ergometry in pediatric ages and teachers in school physical training to meet in separate conferences or symposia to discuss common problems and new research results. During the International Seminar in Ergometry in Berlin in 1967 participants interrested in child age and growth, decided to arrange separate meetings. Thus, a *Pediatric Group on Work Physiology* was founded and arranged an initial symposium in Dortmund in 1968 with Professor J Rutenfranz as chairman. In 1969 the group met in Prague papers were published in Proceedings of the Second Symposium of Pediatric Group of Working Physiology (Ed M. Mácek, Universita Karlova, Praha 1970) The meetings have shown that they have become necessary for ergometry research and pediatric physical training research.

The main topic for the 3rd Symposium, which was held in the Department of Pediatrics of the St Göran s Children s Hospital Stockholm Stockholm in September 1970 were I *Methods of ergometry in children* II. *Clinical aspects of physical training in children* III. *Muscular metabolism during exercise*

Papers read at this symposium are being published in this supplement with one part for each of the three sessions. There are original articles and shorter preliminary communications of importance for the field as well as review articles. As an introduction to the main topics, invited speakers gave key-note papers which also will provide the reader with easier access to information about work physiology and its possibilities for pediatrics today

An increase in our knowledge is not only of importance for the understanding of the physiology of exercise during childhood, but may contribute also to the use of ergometry for functional examinations in pediatrics and to use physical training as a rehabilitation therapy for handicapped or chronically ill children.

Stockholm, March 1971

Claes Thorén, M D
Editor

Acta Paediat Scand Suppl 217 1971

DEFINITIONS, TESTING PROCEDURES, ACCURACY AND REPRODUCEABILITY

PER-OLOF ÅSTRAND

Department of Physiology Gymnastik och Idrott högskolan Stockholm

DEFINITIONS

Efficiency of oxygen transport system There is and has always been some confusion in terminology I would not say particulary evident in the field of work physiology but this area is definitely not expected. If I look back on the titles of our own publications we started to present thoughts about physical working capacity than maximal aerobic capacity and recently maximal aerobic power All the time the emphasis was on the individual's maximal oxygen uptake during exercise. In my opinion the term physical working capacity is often too vague. What type of work should one regard? Capacity does not include the time unit. Therefore aerobic capacity is neither a good expression of oxygen uptake per minute. I think that everyone could agree on aerobic power as an acceptable substitute for oxygen uptake per minute. Aerobic power applies to both submaximal and maximal conditions and therefore we should write maximal aerobic power when the maximal level is considered. So, in our definition maximal oxygen uptake, or *maximal aerobic power* = the highest oxygen uptake the individual can attain during physical work breathing air at sea level. Some objective criteria are necessary to establish that maximum has been reached, and the most objective one is that there is no further increase in oxygen uptake despite further increase in work load.

Physical fitness is another poorly defined expression and it is always a question of "fitness for what?" In physical education in school many teachers and also researchers apply various fitness tests, including evaluation of flexibility skill, strength, etc. related to special gymnastic or athletic performance. They are really not suitable for an analysis of basic physiological functions. Practice and training in the performance of the actual test may greatly influence the results. The Kraus-Weber test may serve as an example. According to the results of studies in which the Kraus-Weber test was used. American girls and boys were definitely inferior to European children. However, the activities included in the test are typical for activities commonly used in European physical education classes. This placed the European children at an advantage over the American ones. Had the testing procedure included activities popular in the United States, the results might have been reversed, rating the American children superior to the European.

The fact that there may be significant correlation between the results from complicated test batteries applied to a group of individuals, or that the scores are related to certain parameters characteristic of the subjects, does not necessarily mean a direct relationship Such data may cause confusion rather than solve problems. From a physiological and medical viewpoint, any test battery for the evaluation of physical fitness is rather meaningless unless it is based on sound physiological consider

ations. The widespread use of such test batteries in physical education can be justified from a pedagogic and psychological viewpoint.

It may help the teacher or coach to stimulate the student's interest in his training. Furthermore, any progress can be evaluated objectively. The selection of such activities and tests should therefore be based on pedagogic and psychological considerations with adaptation to local facilities. If they cannot be justified from these viewpoint it is better to exclude them from the curriculum altogether. Too often the tests are incorrectly claimed to serve a physiological purpose. Actually, from a physiological viewpoint, application of a test battery may sometimes be unsuitable, since the performance of the test usually demands maximal exertion of a subject who may be completely untrained.

It may be concluded that test batteries represent applied psychology and may have no physiological foundation.

Training condition can hardly be evaluated from single examination of muscular, circulatory, etc. responses to various tests. A high maximal aerobic power may be attained in a completly untrained individual and, vice versa, a well-trained subject may score poorly. Quantitatively the genetic factors, the natural endowment, usually play a more important role for the performance than does the individual's training condition.

PROCEDURES

In laboratory experiments three methods of producing standard work loads have mainly been applied: walking or running on a treadmill, working on a bicycle ergometer, and using a step test. I would like to take this opportunity to present our latest "toy": an aquatic swimmill which gives us nice facilities to study the physiology of swimming (movie). Ideally any test of the oxygen transport system should, at least meet the following general requirements: (1) the work in question must involve large muscle groups, (2) the work load must be measurable and reproducible, (3) the test conditions must be such that the results are comparable and repeatable, (4) the test must be tolerated by all healthy individuals, and (5) the mechanical efficiency (skill) required to perform the task should be as uniform as possible in the population to be tested.

The magnitude of the external work can be expressed exactly and it may be reproduced with a high degree of accuracy in the case of the bicycle ergometer and the treadmill. For these reasons the use of the bicycle ergometer or the treadmill is preferable to that of the step test. The treadmill is preferable in studies of young children below the age of 12 and also when it is important to establish the absolute maximal oxygen uptake of the subject.

It appears namely that by running on the treadmill upphill ($\gtrsim 3°$ inclination) the O_2 uptake may be brought to a maximum, while running horizontally or at a slight inclination results in a somewhat lower maximal O_2 uptake. Taylor *et al.* conclude: "Raising the grade with the speed constant (7 mph) is the more satisfactory method of increasing work load with the motor driven treadmill to attain a maximal oxygen uptake."

Bicycling produces, on the average, a lower O_2 uptake, *at least* compared to running *uphill*. In studies in which objective criteria have been used to determined whether or not the maximal O_2 uptake had been reached for the type of work in question, the values for running are on an average 5 to 8 percent higher than for bicycling.

It is not possible at present to explain the reason for the somewhat higher oxygen uptake when running uphill compared with running horizontally or bicycling. It can hardly be caused by the activation of a larger muscle mass during running uphill, since simultaneous work with both arms and legs does not increase the maximal aerobic effect compared with work with the legs only. The higher work tempo during running may enhance the venous return, but if this is the case, running uphill should not be more advantageous than running horizontally.

During bicycling a feeling of local fatigue may often be experienced or a sensation of pain in the thighs or knees, which may be disturbing. This may cause the work effort to be interrupted before the oxygen-transporting organs have been fully taxed.

The work position is of critical importance. The subject should be sitting almost vertically over the pedals. The seat should be high enough so that the leg *is almost completely stretched* when the pedal is in its lowest position. The pedal frequency should be about 60 rpm. In the submaximal exercise test the perferable instruments is, in my opinion the bicycle ergometer. The technique involved is simple. The caloric output or the oxygen uptake can be predicted with greater accuracy than for any other type of exercise. Within limits, the mechanical efficiency is independent of body weight. This is a definite advantage in studies which require repeated examinations over the years. The work *load can, however simply* be selected according to the subject's gross body weight, calculated lean body mass, etc. (for example, 5 or 10 kpm/min×kg). The bicycle ergometer operated with a mechanical brake is inexpensive (e.g., "Monark" bicycle ergometer). It is easy to move from place to place, and is not dependent on the availability of electrical power. Since the subject on the bicycle ergometer exercises in a sitting or lying position with arms and chest relatively immobile, it is quite simple to obtain good ECG tracings and to perform studies with indwelling catheters. During submaximal work a pedal frequency of from 40 to 50 revolutions/min produces the lowest O_2 uptake i.e. the greatest mechanical efficiency. We usually apply 50 rpm and during maximal tests often 60 rpm. Normally a test of maximal aerobic power starts with *a submaximal load which also serves as* a warming up activity. After this the load may be increased in one of several ways: (1) The load may be immediately increased to a level which in preliminary experiments has been found to represent the predicted maximal load for the subject. (2) The load may be increased stepwise with several submaximal maximal, or supermaximal loads, the subject working *5 to 6 min at each load,* with or without resting periods between each load. (3) The load may be increased stepwise every or every other minute until exhaustion. When any one of these procedures is carefully conducted, they give the same maximal oxygen uptake.

From a physiological viewpoint the second method (2) is preferable. It is often of interest to obtain steady-state conditions when measuring oxygen uptake, pulse rate ventilation, etc. at sub*maximal work loads. This requires a work period* of at least 5 min. The more or less continuously increasing work load (procedure 3) is a quick method which may reveal the subject's maximal oxygen uptake. However since steady-state conditions are not attained at submaximal work, this procedures does not provide reliable information as to how the oxygen-transport problem is solved at different levels of physical effort, a type of information which may be of considerable interest.

ACCURACY AND REPRODUCEABILITY

The standard deviation in mechanical efficiency during bicycling is of the order ±6 % in individuals who are not too obese. In other words, the oxygen uptake during a submaximal work on a bicycle ergometer can be predicted with a reasonable accuracy from the work load. In a step test or treadmill test the coefficient of variation in oxygen uptake per kg body weight at a given rate is greater or about 15 %. Therefore it is more important to measure the oxygen uptake in those tests in order to establish the load on the oxygen-transport system. In longitudinal studies it may be a disadvantage that the work load is dependent on the body weight in walking, running and stepping.

There is particularly one source of errors which I think is too often neglected in bicycle tests. There are many reports dealing with the calibration of bicycle ergometers. Cumming and Alexander (1968) point out that the work required to operate several of the electronic ergometers in the market may differ as much as 20 % from the factory calibration. The compensation for various cycling speeds may be over 10 % in error. I am afraid that in general the electronic ergometers are not calibrated often enough, *i.e.* minimum twice a year.

The calibration of the mechanically braked ergometer with a weighted pendulum calibrates the braking force on the wheel with a good accuracy but it does not take into account the frictional resistance of the chain drive, which is as low as

20 kpm at low loads, but as high as 175 kpm at high loads. Therefore a work load of 600 kpm is actually 650 kpm, and of 1200 is actually 1300 kpm/min. This added load must be considered when comparing work load, on such mechanically braked ergometers, e.g. the Monark, and calibrated electronically braked ergometers. It should be emphasized that classical figures for mechanical efficiency i.e. oxygen uptake at given work loads, have been based on data obtained on mechanically braked ergometers assuming a negligible friction effect.

There is one definite advantage always to measure the oxygen uptake during the work test, and then other functions studied can be related to the aerobic power. If so the work load in watts in bicycle or steptest, or speed and inclination of a treadmill is of less importance to know exactly. Considering individual variations in mechanical efficiency and the inaccuracy of many bicycle ergometers I find it illogical to evaluate the fitness of the oxygen transport system by expressing it in watts or kilopond meters per minute at heart rate 170.

In this my introduction I will not comment on the evaluation of results from submaximal test, prediction of maximal oxygen uptake, etc. Only it should be emphasized that it is particularly intricate to interprete data obtained in children aged, say 12 to 16. We can expect improved physical performance just because there is during those years an increase in body size. If we compare animals of different size, it is quite evident that certain dimensions and functional capacities are determined by fundamental mechanical necessities. In addition it may be a matter of biological adaptation. In the children we must thus consider the maturity of the neuromuscular function, improving coordination, and the sexual maturity. This maturity starts at different age, so a grouping a subjects according to age may be misleading. Finally a somewhat fatalistic remark. There are many testing procedures in use and there is still a lack of agreement as far as standardization is concerned. It is inevitable, however, since the inventors of most tests are still alive! Prestige enters the picture. In the future when the next generation will take over, there will be a better chance for agreement on best methods of ergometry in children and adults.

REFERENCES

Astrand, P.-O. & Rodahl, K. *Textbook of Work Physiology.* McGraw Hill, New York, 1970.

Cumming, G. R. & Alexander, W. D. The calibration of bicycle ergometers. *Can. J. Physiol. Pharmacol.* 46: 917. 1968.

DETERMINATION OF W_{170} AND MAXIMAL OXYGEN UPTAKE IN CHILDREN BY DIFFERENT METHODS

R. MOCELLIN, H. LINDEMANN, J. RUTENFRANZ and W. SBRESNY

From Institute für Arbeitsmedizin der Just. Liebig-Universität Giessen, Germany

The determination of maximal oxygen uptake is burdened by difficulties especially during infancy because less trained children can hardly be motivated to bring about maximal effort. There are also some reasonable objections against the participation of sick children in such experiments. Thus, it is much interest in those methods, which permit an estimation of maximal oxygen uptake by means of submaximal measurements. But also the direct report of submaximal criteria, as for instance the W_{170} can be reasonable under these circumstances, especially when the amount of information is not increased through further extrapolation. The commonly used methods of the indirect determination of maximal oxygen uptake have been validated against adults and some of the methods cannot be accepted for use in children without modifications. Therefore, after having done the necessary adjustments, it seemed to be necessary both to check the accuracy of several indirect methods of determination on children and to find out whether the amount of information obtained by means of indirect determination of maximal oxygen uptake is greater than the one obtained by determination of W_{170}. Further we intended to compare the results received by continuously and by stepwise increasing loads.

METHODS

For this purpose we determined at 19 trained boys, 13—14 years of age, at the same time W_{170} and the maximal oxygen uptake, both with stepwise and continuously increasing loads on the bicycle ergometer. The continuous increase of the load was regulated automatically. Up to a pulse rate of 170/min it was 60 kpm/min, beyond this point, till the assessment of the maximal O_2-uptake it was 120 kpm/min.

In case of stepwise increasing loads we chose the performance levels of 240, 480 and 720 kpm/min which correspond to average loads of 1, 2 and 3 Watt/kg body weight. Each period of work lasted 6 minutes. After the third period the load was increased by 120 kpm/min at the beginning of every new minute until the maximal oxygen uptake was reached. Our criteria for the assessment of maximal oxygen uptake were blanching or cyanosis of the extremities, breathlessness, strong engagement of the auxiliary respiratory muscles, gradual reduction of the ability of maintaining exactly the work rate demanded by an optical pacemaker, an obvious levelling of the continuously registered heart frequency.

In order to compare the accuracy of the two methods, we carried out double determinations with stepwise and continuously increasing loads. Every subject then carried out altogether 4 experiments during 2 weeks. The subjects started alternatively with one of both methods in order to avoid training effects upon the result.

The heart rates were continuously summed up by

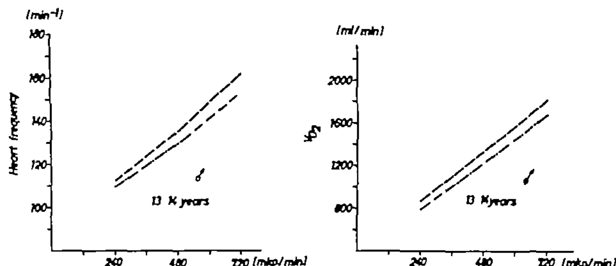


Fig. 1. Heart rate and O_2-uptake in relation to work load at stepwise ( ) and at continuous ( ) with 60 kpm/min increase of load.

an automatic recorder over the R peak of the ECG the sum was printed out every half-minute so that we were able to determine the average heart rate during half or whole minutes. The expired air was collected in Douglas-bags in the following manner at 240 480 and 720 kpm/min for one minute, at higher levels of work load for half a minute. The volume of the expired air was determined by means of a wet gas-meter the CO_2-content of the expired air was determined by means of ultra-red absorption and the content of O_2 was measured on paramagnetic basis.

RESULTS

As shown in Table 1 between the mean values of the first and second determinations concerning both the maximal oxygen uptake and the W_{170} almost no differences could be found. Neither the two methods of determination of the maximal oxygen uptake did result in substantial differences. On the other hand however we found between the values of W_{170} a systematic difference of nearly 100 kpm/min dependent on whether the values had been obtained at continuous or at stepwise increase of loads.

As Figure 1 demonstrates, the reason for this difference between the values of W_{170} is that at nominally equal performance levels, the pulse frequency is lower at continuously increasing loads than the one at stepwise increasing work loads. Corresponding to this result, still in reference to the same figure, the consumption of oxygen is less at continuously increasing loads than at stepwise increasing loads—work loads being nominally equal. During stepwise increasing load O_2-uptake was related to work load as follows

V_{O_2} [ml/min] = 2 W [kpm/min] + 270 (1)

Referring to continuously increasing work load the equation was

V_{O_2} [ml/min] = 1,87 W [kpm/min] + 230 (2)

Using a relation between oxygen consumption and heart rate, the observed differences between pulse frequency and oxygen consumption upon nominally qual performance levels can be almost equalized (see Figure 2)

According to this result it could be expected that, by a relation between oxygen and pulse frequency an indirect determination of the maximal oxygen uptake would lead to nearly the same results, no matter which method of determination was used.

When the regression was extrapolated to the mean maximal heart rate which was 195/min for our experimental group the thus indirectly deter

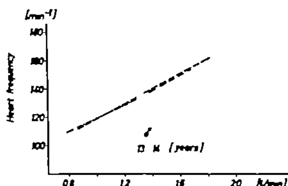


Fig. 2. Heart rate related to O_2-uptake at stepwise and at continuous increase of load. Symbols as in Fig. 1.

mined maximal oxygen uptake value was 2.41 l/min, which was distinctly lower than the mean value of the directly determined maximal O_2-uptake of 2.82 l/min shown in Table 1. Similar results have been communicated by Maritz *et al.* (3) and are based upon the nonlinear relationship between O_2-consumption and work load in the upper performance section. In this section O_2-consumption increases more with increasing work load than heart rate does. In order to equalize the difference between indirectly determined and directly determined maximal O_2-uptake for our experimental group it was necessary to multiply the indirectly determined values of the maximal O_2-uptake with the factor 2.82 : 2.41 = *1.17*.

For the indirect determination of the maximal O_2-uptake we used the methods described by Astrand (1), Müller (4), Margaria *et al.* (2) and Rutenfranz (5). If necessary, we adjusted them to the conditions we encountered in our own experiments. Thus, we applied to the following equations:

Astrand (As) $\dot{V}_{O_2}max$ [l/min] = $\left[\frac{195-69}{HF-69} \times (F \times W + BMR)\right] \times 0.001 \times 1.17$ (4)

Müller (Mü) $\dot{V}_{O_2}max$ [l/min] = $\left[\frac{110}{b} \times F + BMR\right] \times 0.001 \times 1.17$ (5)

Table 1. *Maximal oxygen uptake and W_{170} at double determination by t method*
(n=19)

Type of load		V_{O_2} max l/min AM Mean	S.D.	W_{170} kpm/min Mean	S.D.
stepwise	I	2.81	0.58	819	193
	II	2.79	0.62	824	194
continuously	I	2.85	0.59	919	189
	II	2.84	0.59	916	184

Margaria (Ma) $\dot{V}_{O_2}max$ [l/min] = $\left[\frac{195-(HF_1-b \cdot W_1))}{b} \times F + BMR\right] \times 0.001 \times 1.17$ (6)

Rutenfranz (Ru) $\dot{V}_{O_2}max$ [l/min] = $\left[\frac{195-(\frac{\Sigma HF - b \cdot \Sigma W}{n}}{b} \times F + BMR\right] \times 0.001 \times 1.17$ (7)

where HF are the heart rates upon the corresponding work loads W [mkp/min], F the factor for conversion of work load to O_2-consumption, which has the values 2 at stepwise increasing load and the value 1.87 at continuously increasing load (corresponding to formulas 1 and 2), BMR the basal metabolic rate, determined by means of schedulas or taken as a constant value, b the regression coefficient between work load and heart rate, n the number of heart rate values used for calculation.

Table 2 shows the mean values of the calculated maximal oxygen uptake. The different procedures yielded approximately the same results, both concerning th comparison of first and second determinations and the values which have been found with stepwise and continuously increasing loads. This result however only means, that the different indirect procedures do not show any substantial systematic errors.

Table 3 represents the coefficients of validity of the indirect procedures. Except the coefficients cal

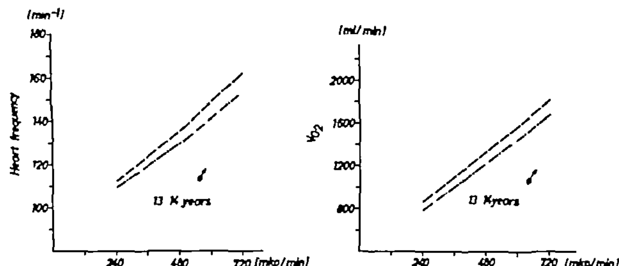


Fig. 1 Heart rate and O_2-uptake in relation to work load at stepwise ( ) and at continuous ( ) with 60 kpm/min increase of load.

an automatic recorder over the R-peak of the ECG the sum was printed out every half-minute so that we were able to determine the average heart rate during half or whole minutes. The expired air was collected in Douglas-bags in the following manner at 240, 480 and 720 kpm/min for one minute, at higher levels of work load for half a minute. The volume of the expired air was determined by means of a wet gas-meter, the CO_2-content of the expired air was determined by means of ultra red absorption and the content of O_2 was measured on paramagnetic basis.

RESULTS

As shown in Table 1, between the mean values of the first and second determinations concerning both the maximal oxygen uptake and the W_{170} almost no differences could be found. Neither the two methods of determination of the maximal oxygen uptake did result in substantial differences. On the other hand however, we found between the values of W_{170} a systematic difference of nearly 100 kpm/min dependent on whether the values had been obtained at continuous or at stepwise increase of loads.

As Figure 1 demonstrates, the reason for this difference between the values of W_{170} is that at nominally equal performance levels, the pulse frequency is lower at continuously increasing loads than the one at stepwise increasing work loads. Corresponding to this result, still in reference to the same figure, the consumption of oxygen is less at continuously increasing loads than at stepwise increasing loads—work loads being nominally equal. During stepwise increasing load O_2-uptake was related to work load as follows

V_{O_2} [ml/min] = 2 W [kpm/min] + 270 (1)

Referring to continuously increasing work load the equation was

V_{O_2} [ml/min] = 1.87 W [kpm/min] + 230 (2)

Using a relation between oxygen consumption and heart rate, the observed differences between pulse frequency and oxygen consumption upon nominally equal performance levels can be almost equalized (see Figure 2).

According to this result it could be expected that, by a relation between oxygen and pulse frequency an indirect determination of the maximal oxygen uptake would lead to nearly the same results, no matter which method of determination was used.

When the regression was extrapolated to the mean maximal heart rate which was 195/min for our experimental group the thus indirectly deter-

t can be assumed that the validity of the indirect methods of determination actually is still somewhat higher than it seems to be according to the validity coefficients we have found.

SUMMARY

1 Upon nominally equal levels of performance there exist differences in heart rate which result in different values of W_{170}. These differences depend upon the method of determination.

2. The differences can be reduced by relating heart rate to O_2-uptake. Indirect calculations of maximal O_2-uptake based on this relation lead to approximately equal values independent of what kind of load-increase is used.

3 The maximal O_2-uptake is underestimated by the indirect procedures therefore the values must be adjusted by a factor.

4. On the basis of 1 or more measurements the maximal O_2-uptake can be estimated with near ly equal accuracy

5 Procedures where the starting pulse frequency remains the same (1 4) must be adjusted to the conditions prevailing in infancy

6 The cardio-vascular performance capacity can be estimated equally well both by means of W_{170} and indirect calculations of maximal O_2-uptake.

7 The direct determination of the maximal O_2-uptake is also open to certain errors which have a negative influence upon the validity of the indirect procedures.

REFERENCES

1 Astrand, P-O and Rhyming, I. A nomogram for calculation of aerobic capacity from pulse rate during submaximal ork. *J Appl Physiol* 7 218, 1954.

2. Margaria, R Aghemo, P and Rovelli, E. Indirect determination of maximal oxygen consumption in man. *J Appl Physiol* 20. 1070, 1965

3 Maritz, J S Morrison, J F Peter J Strydom, N B and Wyndham, C. H. A practical method of estimating an individual' maximal oxygen uptake. *Ergonomics* 4 97 1961

4 Müller E. A. Die ärztliche Beurteilung der körper lichen Dauerleistungsfähigkeit im Beruf. *Dtsch Med Wschr* 86. 2272, 1961

5 Rutenfranz, J Exercise tests in children and adolescents *I* Lange Andersen, K., Shephard, R. J. Denolin, H., Varnauskas, E., and Masironi, R. (ed.) Fundamentals of exercise testing P 105—109 WHO Geneva (1971)

(R M.) Universitäts-Kinderklinik
8 München 15
Lindwurmstr 4
Germany

Key words. Physical fitness, maximal oxygen uptake.

DIRECT AND INDIRECT ESTIMATION OF MAXIMAL OXYGEN UPTAKE IN PRE PUBERTAL BOYS

LARS HERMANSEN and SVEIN OSEID

From the Institute of Work Physiology and Pediatric Research Institut University Hospital Rikshospitalet Oslo, Norway

INTRODUCTION

Maximal oxygen uptake has been widely used as an index physical performance (2, 8, 14) as it gives valuable information about both the functional capacity of the oxygen transport system and also the maximal aerobic work power of the subjects.

Measurements of maximal oxygen uptake when obtained under properly standardized conditions are known to be a highly reproducible parameter (12, 14) However the procedure requires almost maximal effort and considerable motivation of the subjects. Thus, it is not commonly used in very young and elderly individuals nor in patients.

Furthermore, the determination of the maximal oxygen uptake is a time consuming procedure both for the investigator and the subjects. Consequently it is important to develop a test which will give a reliable and acurate estimate of the individuals maximal oxygen uptake, using submaximal effort. In fact, several submaximal test procedures have been developed in many exercise laboratories (10 11 18 20)

Astrand and Ryhming (3) have constructed a nomogram by which maximal oxygen uptake is calculated from heart rate at submaximal work load. The accuracy of this method has been studied in young healthy students (7) and in older subjects (17) However longitudual studies over a longer time period (i.e. 3 years) have not been performed to investigate the accuracy of the Astrand and Ryhming method. Furthermore, to our knowledge such studies have not been undertaken using school-children as experimental subjects. The aim of the present study therefore, was to compare the values for maximal oxygen uptake measured directly by using the classical Douglas bag method with the values obtained using the indirect Astrand and Ryhming method in the same group of subjects for three consecutive years.

MATERIAL AND METHODS

Altogether 70 prepubertal boys from the same class in one of the schools in Oslo were studied for three consecutive years. Average values for age and weight are given in Table 1

The subjects came to the laboratory in the post absorptive state, and were studied between 2 and 4 p.m.

Two methods were used to measure the maximal oxygen uptake, the indirect and direct method (see below)

In all subjects maximal oxygen uptake was calculated from measurements of heart rate and work load according to the method described by Astrand and Ryhming (3) i.e the indirect method The values for maximal oxygen uptake obtained by this method were corrected for differences in maximal heart rat as suggested by Astrand (1) The ex

Table 1 *Maximal oxygen uptake (direct and indirect method) and maximal heart rate in pre-pubertal boys. Mean values and range*

Age years	Weight kg	Max. O_2-uptake Direct method liter/min	ml/kg×min	Indirect method liter/min	ml/kg×min	Maximal heart rate beats/min	Max. O_2-uptake Ind. meth. corr liter/min	ml/kg×min
10.5	36 0 28 6—44.7	1.96 1.57—2..6	54.3 46—62	1.59 1 3—2 0	45.2 35—58	205 9 194—217	1.63 1 48—2 11	48.1 39—59
11.5	39 9 31.6—51.1	2 17 1.74—2.61	54.7 48—62	1 92 1 5—2.3	48.6 31—57	202 8 190—214	2.03 1 57—2.35	51 4 34—61
12.5	43.6 35 2—56 2	2.32 2 04—3 40	58 1 48—66	2 13 1 8—2 8	49 6 36—63	202 6 187—212	2.24 1 97—2 81	52.1 37—69

periments were performed on a mechanically braked bicycle ergometer described by von Döbeln (6). The height of the saddle on the bicycle ergometer was adjusted to each individual to ensure a slight bending of the knee when the anterior part of the foot was placed on the pedal in its lowest position. The pedal rate was kept constant at 50 revolutions per min by using a conventional metronome.

Maximal oxygen uptake was also determined directly by using the Douglas bag method. All direct determinations of maximal oxygen uptake were performed on a motor-driven treadmill. The subjects were running uphill (3 or 5.25 %) at a speed which lead to exhaustion within 4—6 min.

In general the procedure suggested by Hermansen and Saltin (9) was used in all determinations. The maximal experiments on the treadmill started with a 10 min of warming up on a work load representing 50—70 % of the predicted maximal oxygen uptake of the individual.

The expired air was collected in a series of Douglas bags during the last minute of the maximal exercise, until the subjects were completely exhausted. The collected volume of expired air was measured a spirometer and gas analyses were performed in duplicate on a Scholander apparatus (15). The respiratory valve had dead space of 100 ml. The inner diameter of the valve, the stop-cock and the tube of the Douglas bags was 30 mm. The connecting tubes were smooth and not corrugated, with an inner diameter of 35 mm. The length of the connecting tube, from the subject to the bag was approximately 50 cm. Heart rate was continuously recorded during the air collection period by using a conventional electro-cardiogram apparatus.

Blood lactate concentration was measured in samples taken during the first 5 min after the maximal run, and analyzed according to the method of Baker and Summerson as modified by Ström (16). The data for blood lactate concentration are not presented in the results, but are included together with the values for maximal heart rate as supporting criteria in the evaluation of the maximal oxygen uptake measurements, as proposed by Åstrand (2).

RESULTS

Mean values and range in liter/min and ml/kg ×min for the measured maximal oxygen uptake (direct method) and the calculated maximal oxygen uptake (indirect method) are given in Table 1. The values for maximal heart rate and the corrected values for maximal oxygen uptake (indirect method) are also given in Table 1. The calculated values for maximal oxygen uptake were found to be 0.37, 0.25 and 0.39 liter/min or 19 %, 12 % and 15 % lower than those observed with the direct method for the 3 consecutive years (i.e. age 10.5, 11.5 and 12.5 years), respectively.

When the calculated values were corrected for differences in maximal heart rate, a somewhat smaller difference was observed. The mean difference (±SE) between the direct and the indirect estimations of maximal oxygen uptake was then 0.33±0.04, 0.14±0.4 and 0.28±0.06 liter/

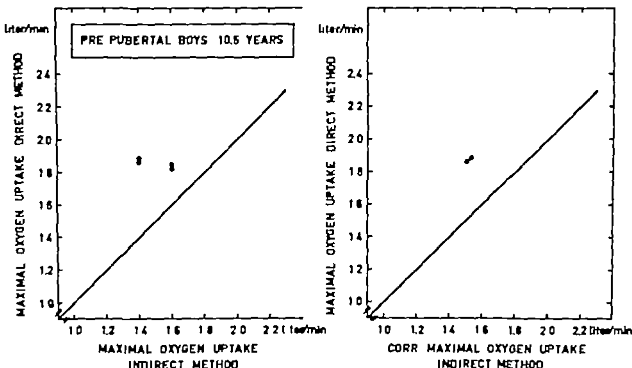


Fig 1 Individual values for maximal oxygen uptake measured during maximal running (i.e. direct method) in 20 pre-pubertal boys at the mean age of 10.5 years are plotted against the corresponding values obtained by the indirect method (i.e. calculated from heart rate at a given submaximal work load) in the left panel, and against the corresponding calculated values after correction for differences in maximal heart rate (right panel)

min, respectively Thus, even after correction for the differences in maximal heart rate, the calculated values were approximately 17 %, 5 % and 11 % lower than the mean values obtained with the direct method for the three different years.

Individual values for maximal oxygen uptake (indirect method) and the corrected indirect values are plotted against the corresponding values for maximal oxygen uptake obtained by the direct estimations in Figs. 1—3 The values from the first investigation (average age=10 5 years) are given in Fig 1 while the values for the second and third year are given in Figs. 2 and 3

It should be noted (Figs. 1—3) that although the mean values for the direct and indirect methods as given above showed a fairly good agreement, the individual differences between the measured and the calculated values for maximal oxygen uptake are considerable.

DISCUSSION

The main objective of the present study was to compare the values for maximal oxygen uptake measured during maximal running with those obtained by using the Astrand and Ryhming nomogram. The average values for the predicted maximal oxygen uptake were found to be approximately 10—20 % lower than those measured during maximal exercise Our findings on pre-pubertal boys are substantial in agreement with earlier reports using adults as experimental subjects (5 7) However although the average values for maximal oxygen uptake showed a fairly good agreement, it should be noted that the individual difference between the measured and the calculated values varied considerably

The explanation for these variations is not known As pointed out by several authors (4 12, 17) there are considerable sources of errors in

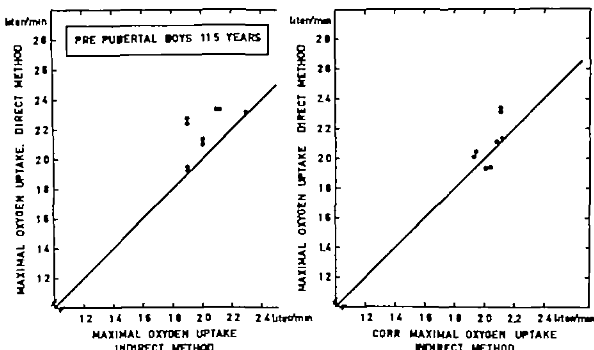


Fig 2. Individual values for maximal oxygen uptake (direct method) in 20 pre-pubertal boys at the mean age of 11 5 years are plotted against the corresponding values obtained by the indirect method (left panel) and against the indirect values after correction for differences in maximal heart rate (right panel) For further explanation see legend to Fig 1 and text

any prediction of maximal oxygen uptake from submaximal effort. It should be noted that the Astrand and Ryhming method used in the present investigation is a prediction of maximal oxygen uptake from measurements of heart rate during submaximal work loads with an extrapolation to a maximal herat rate of 195 beats/min.

Consequently in subjects with a maximal heart rate above 195 beats/min, the predicted values for maximal oxygen uptake will be underestimated i.e. lower than those obtained during maximal treadmill running In the present study the average heart rate was found to be 205 9 202.8 and 202.6 for the three different years, respectively When the predicted valuesfor maximal oxygen uptake were corrected for differences in maximal heart rate, as suggested by Astrand (1) somewhat smaller differences were observed.

However even after correction of differences in maximal heart rate the predicted values for maximal oxygen were markedly lower than the measured values. Thus, variations in the maximal heart rate could not explain more than a fraction of the total difference, observed between the two methods.

Another important factor which might influence the prediction of maximal oxygen uptake, is the estimation of oxygen uptake during the submaximal exercise. In the present study the oxygen uptake was not measured during the submaximal bicycle exercise, but estimated supposing a fixed mechanical efficiency As pointed out by Astrand and Rodahl (4) part of the difference between the pre dicted and the measured values for maximal oxygen uptake may be explained by intra-individual variations in the mechanical efficiency However since oxygen uptake was not measured during the submaximal bicycle exercise, it is not possible to evaluate the relative contribution of this factor

From several studies it appears that a number of situations may influence the heart rate/oxygen up-

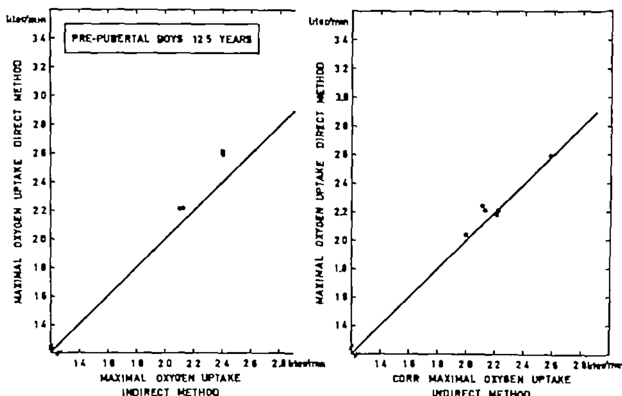


Fig. 3. Individual values for maximal oxygen uptake (direct method) in 20 pre-pubertal boys at the mean age of 12.5 years are plotted against the corresponding values obtained by the indirect method (left panel) and against the indirect values after correction for differences in maximal heart rate. For further explanation see legend to Fig. 1 and text.

take relationship during submaximal exercise, without any significant change in the maximal oxygen uptake values (12, 13, 19). In the present investigation, however, care was taken to minimize the effects of these factors. All submaximal exercise tests were performed after at least 1 hour rest, and approximately 2—3 hours after a light meal. Rectal temperature was measured at the end of the rest period to ensure that the subjects were free of any infection. Furthermore, the temperature in the laboratory was kept between 18—20° and the subjects had not been engaged in heavy muscular exercise during the last 48 hours. Thus, it is not likely that these factors would influence the predicted values for maximal oxygen uptake more than to a minor extent.

From the results of the present investigation in 20 pre-pubertal boys, it can concluded that the calculated values for maximal oxygen uptake were in average approximately 15 % lower than the values obtained during maximal running on the treadmill. When the calculated values were corrected for differences in maximal heart rate, the difference was reduced to in average 11 %.

Thus, even when the test is performed under carefully standardized conditions, the methodological error in predicting an individual's maximal oxygen uptake is considerable. However, when one group of subjects is compared with another, there is a fairly good agreement between the values obtained by the direct and indirect method.

SUMMARY

Maximal oxygen uptake was measured directly during maximal treadmill running (3° inclination) using the Douglas bag method and also calculated (i.e. indirect method) from heart rate during submaximal bicycle exercise in 20 prepubertal boys,

once a year for three consecutive years. The calculated values for maximal oxygen uptake were found to be 0 37 0.25 and 0.39 liter/min, or 19 % 12 % and 15 % lower than those with the direct method for the three different years (i.e. age 10 5 11 5 and 12 5 years) respectively When the calculated values for maximal oxygen uptake were corrected for differences in the maximal heart rate, somewhat smaller differences between the two methods were observed (i.e. 17 % 6 % and 11 % for the three years respectively) Thus, intra-individual variations in maximal heart rate could explain only a fraction of the total difference between the two methods. It is concluded that there is fairly good agreement between the average values of the two methods for the whole group (i.e. 20 subjects) However the intra-individual differences are considerable Consequently the indirect method for estimation of maximal oxygen uptake should only be used when accurate individual values are not required.

REFERENCES

1 Astrand, I Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand* 49 Suppl 169 1960

2 Astrand, P-O *Experimental studies of physical working capacity in relation to sex and age* Munksgaard, Copenhagen 1952

3 Astrand, P-O & Ryhming, I A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work *J Appl Physiol,* 7 218, 1954

4 Astrand, P-O & Rodahl, K. *Textbook of Work Physiology* McGraw Hill Book Company New York 1970

5 Chase, G. A Grave, C. & Rowell, L B Independence of changes in functional and performance capacities attending prolonged bed rest *Aerospace Med* 37 1232, 1966.

6 von Dobeln, W A simple bicycle ergometer *J Appl Physiol,* 7 222, 1954

7 Glassford, R G Baycroft, G H Y Sedgwick, A W & Macnab, R B. J Comparison of maximal oxygen uptake values determined by predicted and actual methods *J Appl Physiol.* 20 509 1965

8 Hermansen, L & Andersen, K L Aerobic work capacity in young Norwegian men and women. *J Appl Physiol* 20 425 1965

9 Hermansen, L & Saltin, B. Oxygen uptake during maximal treadmill and bicycle exercise. *J Appl Physiol* 26 31, 1969

10. Margaria, R Aghemo, P & Rovelli, E Indirect determination of maximal O consumption in man. *J Appl Physiol* 20 1070 1965

11. Maritz, J S Morrison, J F Peter, J Strydom, N. B & Wyndham, C. H. A practical method of estimating an individual maximal oxygen uptake. *Ergonomics* 4 97 1961

12 Rowell, L. G Taylor H. L & Wang, Y Limitations to prediction of maximal oxygen intake. *J Appl Physiol* 19 919 1964.

13 Saltin, B. Aerobic work capacity and circulation at exercise in man. *Acta Physiol Scand* 62 Suppl. 230, 1964.

14 Saltin, B & Astrand, P-O Maximal oxygen uptake in athletes *J Appl Physiol,* 23 353 1967

15 Scholander, P E. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. *J Biol Chem* 167 235, 1947

16. Ström, G The influence of anoxia on lactate utilization in man after prolonged muscular work. *Acta Physiol Scand* 17 440, 1949

17 Teräslinna, P Ismail, A. H. & MacLeod, D F Nomogram by Astrand and Ryhming as predictor of maximum oxygen intake. *J Appl Physiol* 21 513 1966.

18 Wahlund, H Determination of the physical work capacity *Acta Med Scand* Suppl 215 1948.

19 Williams, C. B Bredell, G A. G Wyndham, C. H Strydom, N. B Morrison, J F Fleming, P W & Wood, J S. Circulatory and metabolic reaction to work in heat. *J Appl Physiol,* 17 625, 1962.

20. Wyndham, C. H. Submaximal test for estimating maximum oxygen intake. *Canad Med Ass J* 96 736, 1967

(L.H) Institute of Work Physiology
Gydas vei 8, Oslo 3, Norway

Key Word maximal oxygen uptake—prediction of maximal aerobic power—maximal heart rate.

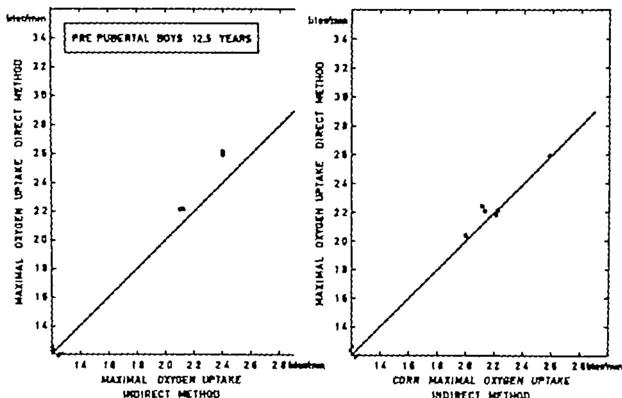


Fig. 3. Individual values for maximal oxygen uptake (direct method) in 20 pre-pubertal boys at the mean age of 12.5 years are plotted against the corresponding values obtained by the indirect method (left panel) and against the indirect values after correction for differences in maximal heart rate. For further explanation see legend to Fig. 1 and text.

take relationship during submaximal exercise, without any significant change in the maximal oxygen uptake values (12, 13, 19). In the present investigation, however, care was taken to minimize the effects of these factors. All submaximal exercise tests were performed after at least 1 hour rest, and approximately 2—3 hours after a light meal. Rectal temperature was measured at the end of the rest period to ensure that the subjects were free of any infection. Furthermore, the temperature in the laboratory was kept between 18—20° and the subjects had not been engaged in heavy muscular exercise during the last 48 hours. Thus, it is not likely that these factors would influence the predicted values for maximal oxygen uptake more than to a minor extent.

From the results of the present investigation in 20 pre-pubertal boys it can concluded that the calculated values for maximal oxygen uptake were in average approximately 15 % lower than the values obtained during maximal running on the treadmill. When the calculated values were corrected for differences in maximal heart rate, the difference was reduced to in average 11 %.

Thus, even when the test is performed under carefully standardized conditions, the methodological error in predicting an individual's maximal oxygen uptake is considerable. However, when one group of subjects is compared with another, there is a fairly good agreement between the values obtained by the direct and indirect method.

SUMMARY

Maximal oxygen uptake was measured directly during maximal treadmill running (3° inclination) using the Douglas bag method and also calculated (i.e. indirect method) from heart rate during submaximal bicycle exercise in 20 prepubertal boys,

A to begin the assignment cycle again. Boys and girls were randomized separately.

Prior to the beginning of the work tests, each child was given instructions and a few minutes of practice to become familiar with walking on the treadmill and wearing the apparatus to collect expired air. After it was determined that each child was able to walk on the treadmill comfortably, he rested for several minutes, during which time procedures were explained. They were then given a 3-minute warm-up period at 3.5 mph (5.6 km/hr) 7.5 % grade. Heart rate was monitored near the end of each minute. This warm-up period was followed by a four-minute rest period, after which each child underwent one of the three tests to determine $\dot{V}_{O_2}$ max.

In Test A, the first work load was 3.5 mph, 10 % grade; this was increased by 2.5 % every two minutes until the subject reached a self-imposed maximum. Heart rate was recorded near the end of each minute and a sample of expired air was taken during the second minute of each work load. Test B used the same procedures as in Test A, except that the grade was increased by 2.5 % every three minutes. Heart rate was recorded near the end of each minute and samples of expride air were taken during the second and third minutes of each work load. In Test C, the subject walked for four minutes at 3.5 mph, 15 % grade after the initial warm up. If he completed the four minutes, he then rested for ten minutes, after which he walked for four minutes at 17.5 % grade. Thus, the grade was increased by 2.5 % (with ten minutes of rest between each work load) until the subject reached a self-imposed maximum. Heart rate was recorded near the end of each minute of exercise and samples of expired air were taken during the second, third, and fourth minutes. All subjects were verbally encouraged to continue as long as possible when they were approaching their maximum so that valid criteria for $\dot{V}_{O_2}$ max could be reached in as many subjects as possible.

RESULTS

There were no significant differences (Table 1) age, height, weight, percent body fat, arm

TABLE 1 *Selected anthropometric strength, intelligence and cardiovascular data obtained on subjects taking three treadmill tests* Mean ±1 S.D.

Test	N	Age (yr)	Height (cm)	Weight (kg)	Body fat (%)	Arm flexion strength (kg)	I.Q.	Heart rate during warm-up 1	2	3
	Boys									
A	31	10.7±2.6	138.6±16.2	33.6±13.1	16.3±4.2	14.9± 3.3	80.1±12.7	144.8±13.2	150.5±13.9	151.4±14.9
B	26	10.9±2.6	138.9±15.5	31.7±12.2	16.5±4.4	14.3± 5.1	79.7±11.9	117.7±14.4	153.1±17.3	154.3±19.1
C	26	10.6±2.3	140.2±12.1	33.7±12.1	17.0±3.9	14.6± 5.5	80.6±10.7	146.7±11.6	152.9±15.1	154.0±16.5
	Girls									
A	21	10.4±2.8	139.0±16.4	37.7±19.8	26.5±5.9	12.9± 4.6	81.3±11.0	154.9±10.0	161.1±13.5	167.3±16.6
B	20	10.4±2.5	138.6±13.1	33.3±11.1	25.0±5.3	12.6± 3.9	77.0±13.6	150.9±12.1	160.0±13.6	163.9±12.9
C	20	10.2±2.8	135.7±13.4	32.4±11.3	25.8±5.1	12.6± 5.7	82.3±13.8	156.4±15.9	165.5±17.3	170.4±18.3

TABLE 2 Maximal values obtained on the treadmill tests and total time required
Mean ±1 SD

Test	N	$\dot{V}_{O_2}$ max (cc/kg min)	HR_{max} (beats/min)	Total time required (min)
	Boys			
A	31	51.6±7.0	197.7±10.1	9.2± 2.6
B	26	50.0±5.5	200.9± 8.5	10.3± 2.8
C	26	53.0±4.3	199.1± 7.5	35.1±12.8
	Girls			
A	21	43.0±6.9	203.0±10.[illegible]	7.2± 2.7
B	20	45.7±5.1	203.5± 6.7	9.4± 2.1
C	20	44.8±6.2	20[illegible].7± 8.7	16.0± 8.9

Test C > Tests A and B ($p < 0.01$)

flexion strength, I Q or in HR response to a standard work load during the warm-up period for the subjects in the three groups. Thus, it appears that these groups were similar. The results from the maximal tests revealed no significant differences in V_{O_2} max (cc/kg min) or HR_{max} with the treadmill tests (Table 2). Because of the ten-minute rest periods between the work loads in Test C, however, significantly more time was required to obtain maximal values. Among each of the four age groups there were no significant differences in maximal values obtained from any of the three tests (Figure 1). A more detailed analysis of variance also revealed no significant differences among tests for maximal values of oxygen pulse, pulmonary ventilation, respiratory quotient or ventilatory equivalent.

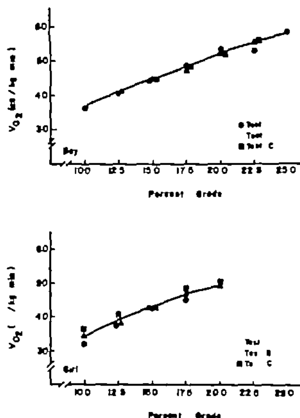


Fig. 2. Oxygen consumption (V_{O_2}) for boys and girls in relation to work load on three treadmill tests, as represented by percent grade at 3.5 mph

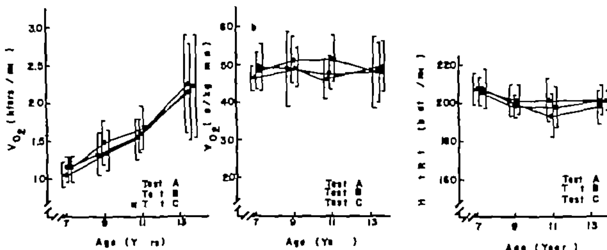


Fig. 1. Maximal values of oxygen consumption (V_{O_2}) and heart rate for three treadmill tests in relation to chronological age

TABLE 2 Maximal values obtained on the three treadmill tests and total time required
Mean ±1 S.D.

Test	N	V_{O_2} max (cc/kg min)	HR_{max} (beats/min)	Total time required (min)
	Boys			
A	31	51.6±7.0	197.7±10.1	9.2± 2.6
B	26	50.0±5.5	200.9± 8.5	10.3± 2.8
C	26	53.0±4.3	199.1± 7.5	35.1±12.8*
	Girls			
A	21	45.0±6.9	203.0±10.2	7.[illegible]± 2.7
B	20	45.7±5.1	203.5± 6.7	9.4± 2.1
C	20	44.8±6.2	202.7± 8.7	16.0± 8.9

Test C> Tests A and B (p <0.01)

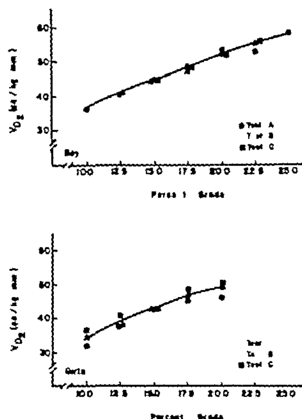


Fig. 2. Oxygen consumption (V_{O_2}) for boys and girls in relation to work load on three treadmill tests, as represented by percent grade at 3.5 mph.

flexion strength, I.Q. or in HR response to a standard work load during the warm up period for the subjects in the three groups. Thus, it appears that these groups were similar. The results from the maximal tests revealed no significant differences in V_{O_2} max (cc/kg min) or HR_{max} with the treadmill tests (Table 2). Because of the ten-minute rest periods between the work loads in Test C, however, significantly more time was required to obtain maximal values. Among each of the four age groups there were no significant differences in maximal values obtained from any of the three tests (Figure 1). A more detailed analysis of variance also revealed no significant differences among tests for maximal values of oxygen pulse, pulmonary ventilation, respiratory quotient or ventilatory equivalent.

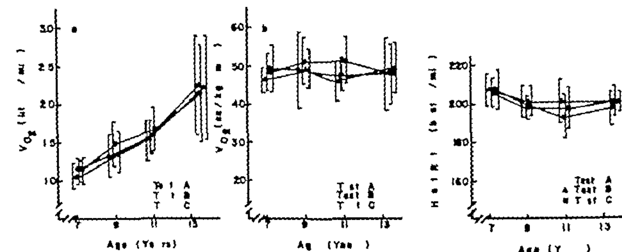


Fig. 1. Maximal values of oxygen consumption (V_{O_2}) and heart rate for three treadmill tests in relation to chronological age.

Acta Paediat Scand Suppl 217 1971

INTERMITTENT EXERCISE OF SUPERMAXIMAL INTENSITY IN CHILDREN

M. MACEK, J VAVRA, & B. MRZENA

From the Laboratory for physical fitness research, Faculty of Pediatrics Charles University, Prague Czechoslovakia

In a recent study (1) we investigated short-term exercise response in a large sampling of the child population, comprising boys and girls from six to fourteen years. We could not find any difference in steady state oxygen uptake at various levels of submaximal workload between boys and girls of the same weight, but there was a striking difference in blood lactate levels, these being distinctly higher in girls in higher weight groups than in boys (Figs 1—2). The question arose whether the higher production of lactid acid in girls is the consequence of less efficient adaptation of the oxygen supply at the very beginning of exercise or whether the lactid acid is permanently produced at higher workload levels since these levels represent a relatively higher load for girls.

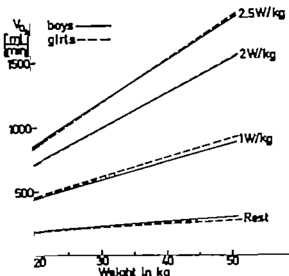


Fig. 1. The oxygen uptake at rest and at different levels of work (watts/kg body weight) in boys and girls.

MATERIAL AND METHODS

The aim of the current study was to elucidate the adjustment of the oxygen supply at the beginning of exercise by following the contributing parameters in boys and girls. For this purpose, a group of 6 boys and 6 girls, all 13-year olds, was subjected to very heavy intermittent exercise (approxi

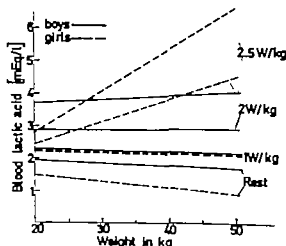


Fig. 2. Blood lactate concentration in the same situation as described in Fig. 1

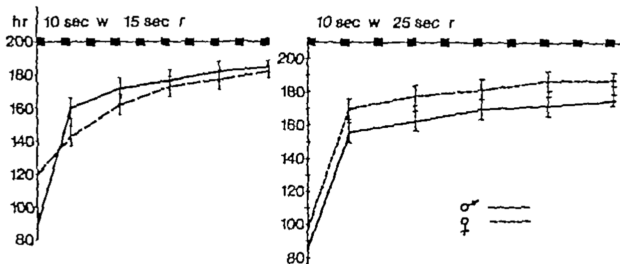


Fig. 3 The mean value (±SE) for the heart rate response beats/min at the end of the work period (10 seconds) in intermittent exercise where the duration fo the est period has been aried from 15 to 25 seconds. The time axis at the top of the graph and the black areas denote each ork period.

mately 5 watts per kg body weight) on the bicycle ergometer. Each subject performed two series of exercise on two successive days consisting of ten 10-sec bursts of pedalling In the first series pauses of 15 seconds duration were interposed, in the second series pauses were of 25 seconds duration. All children were well aquainted with the labora methods, and had repeatedly participated as volunteers.

RESULTS

The results are shown in the Fig 3 Heart rate was recorded continuously with an ECG and was evaluated by means of a cardiotachometer The cardiovascular adjustment showed a prompt increase in heart rate, this being at little steeper in boys than in girls in the first series (10 sec work +15 sec pause) but, with scarcely any difference in final values. In the second series (10 sec work +25 sec pause) the initial acceleration was the same in boys and girls but final values were higher in girls. These values were almost synanymous with maximal heart rate in girls, whereas in boys the values levelled off at lower levels. The results of the first series suggest that cardiovascular adjustment is similar in both boys and girls.

For oxygen uptake determinations, expired air was collected separately i.e.in one cumulative bag for the first five work bursts, in another bag for the last five bursts and in the same manner for the first five interspersed pauses and the last five pauses. Resting oxygen uptake was subtracted from the oxygen uptake in these periods in order to obtain net work oxygen consumption.

Oxygen uptake during work bursts was consistently higher in boys than in girls. The difference between boys and girls increased during the second half of the work, but comparison of oxygen uptake in the first and second work halves showed that the relative increase was the same in boys and girls, the first half amounting to approximately seventy per cent of the final value. This calculation suggests that the process of adaptation does not differ in boys and girls but boys show higher aerobic values. If calculated per minute and per kg body weight, oxygen uptake in work was found to amount to 50.1 ml in boys and 38.4 ml in girls, which is very close to their aerobic capacities.

DISCUSSION

A higher payment of oxygen debt in pause can be found in girls. Our experimental design was similar to that used by Margaria in his studies of energy metabolism at the beginning of exercise

(2) Margaria found that in vere heavy intermittent work with work periods of 10 seconds duration, the magnitude of lactic acid production depends on the duration of the interposed pauses. With pauses lasting more than 20 seconds, no lactate was produced at all, and the exercise could be repeated for a very long time. He calculated that energy requirements for work bursts were completely covered by stores of energy-rich phosphate bonds with their complete resynthesis during every pause. If shorter pauses were interposed, increase in lactid acid was indirectly related to their duration.

To verify this finding in boys and girls, brachial vein blood was sampled after cessation of the work in both experiment series for lactate determination. Values obtained in both series were identical in boys, the influence of different pause durations could not be established. In girls blood lactates values were higher in the series with longer pauses, however, the difference between both series was not significant. But there was a distinct difference in blood lactate levels between boys and girls values for gils were significantly higher in both series.

Bloodlactate concentration in boys was 5.3 ± 1.4 mMol/l in the first series of experiments, 5.3 ± 1.2 mMol/l in the second series, in girls 7.0 ± 2.1 mMol/l in the first series and 8.1 ± 1.5 mMol/l in the second series. The values are significantly lower ($p < 0.001$) in boys than in girls.

In both boys and girls, the increase in blood lactate concentration bears witness to the significant participation of anaerobic lactacid mechanisms during the work bursts, which is of the same intensity irrespective of the length of interposed pauses. The anaerobic mechanisms are more intensive in girls, most probably in connection with the lower aerobic capacity which is not great enough to meet the energy demands of very heavy work to the same extent as in boys.

It is difficult to explain the discrepancy between our results and Margaria's statement. We were unable to show that a pause of 25 seconds duration is long enough to prevent the products of lactacid metabolism from accumulating.

An explanation could be based on the different way of loading. Margaria subjected a group of adults to exercise exercise on the treadmill. It was shown that in treadmill exercise a larger muscle mass is engaged than in bicycle ergometer exercise and that lactic acid production at the same exercise intensity is greater when a smaller muscle mass is engaged. Thus, differences in bicycle ergometer loading could explain the different results.

SUMMARY

The difference between boys and girls stems primarily from the lower aerobic capacity in girls, neccessitating a higher rate of anaerobic energy release. Different mechanism of adaptation to exercise is discussed.

Our results provide evidence of differences in lactacid mechanisms in boys and girls, the riddle of a lactacid mechanisms remaining unsolved.

REFERENCES

1. Máček, M. and Vávra, J. The cardiopulmonary and metabolic changes during exercise in children 6 to 14 years old. J Appl Physiol, 30: 200, 1971.

2. Margaria, R. Oliva, R. D. di Prampero, P. E. and Cerretelli, P. Energy utilization in intermittent exercise of supramaximal intensity. J Appl Physiol, 26: 752, 1969.

(M.M.) Faculty of Pediatrics
Charles University
Praha 5, Motol, V úvalu 84
Czechoslovakia

Key words: Maximal oxygen uptake, blood lactate, intermittent exercise, boys and girls.

TREADMILL EXERTION IN CHILDREN AGED FIVE[1]

FERDINAND KLIMT

From Institut für I f klinisch arbeiten im Kind alter Stadt Klinik m Berlin-Buch, DDR

The treadmill offers wide possibilities of in vestigation in children, in conditions of exercise. Walking and running belong to the daily prevalent physical activities of a child. The use of the tread mill allows to perform this type of exercise in al most physiologic conditions. The fact that the subjects only run on thespot, the work of the ex tensors of the leg thus being comparatively lower must be accepted owing to the advantage of a better reproducibility

With the purpose to carry out such investigations particularly in infants, we previously constructed a treadmill (1) The present paper deals with the results obtained in 48 healthy girls and boys, aged five.

METHOD

At the beginning of the exercise, the children were asked to run horizontally at a speed of 4 km/h during f ve minutes. This corresponds to a distance of 333 m. After 5 min. of recovery the children a new run the same speed during 3 min., however at a 15 slope angle of the treadmill. This would mean that for a distance of 200 m covered in three minutes, a difference level of more than 50 m is to be overcome

The respiratory parameters were recorded by means of a spirograph PANTESTOR (Dargatz, Hamburg) ECG was registered and with the aid of an analogic digital computer (Universalzähler VEB Funkwerk, Erfurt) the duration of the heart periods was detected (Ergebnisdrucker VEB Funk werk, Erfurt) The ventilated air volume was cal culated for BTPS, whereas the oxygen uptake was corrected for STPD The results were classified ac cording to age, body surface, and sex, so as to be evaluated statistically

RESULTS

At the beginning of the horizontal running (4 km/h) the mean oxygen uptake (VO_2) the oxygen pulse, the heart rate, the pulmonary ventilation (V) the respiratory volume (V_T) and the breathing rate increased both in girls and in boys. One minute after starting to run rises of 133 and of 200 % respectively of the oxygen uptake were found in boys and in girls, while the heart rate increased with 27 and 30 % respectively Already after one minute of exercise, the mean values of the heart and respiratory rate were within the confidence limits of the values obtained at any moment during the rest of the first exertion. This is also valid for the other biological parameters such as $\dot{V}_E$, V $\dot{V}O_2$ and oxygen pulse, however from the next minute of activity on. The criteria of ergostase were fulfilled in both groups.

[1] The investigations are part of research project Prophylactic health care children and juveniles of the Ministry of Heal h of he German Democratic Republi

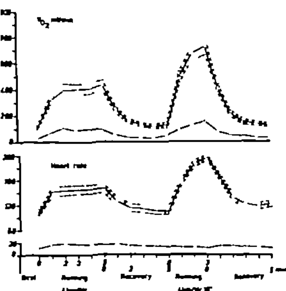


Fig 1 Oxygen uptake (VO_2) and heart rate in girls (n=23) aged 5, at rest during and after treadmill exercise at submaximal and maximal intensity Mean values ±SE. Broken lines at the bottom denote one SD

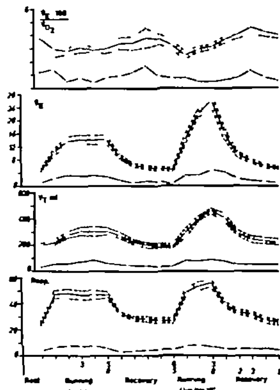


Fig 2. Respiratory equivalent, respiratory minute volume (V_E) tidal volume (V_T) and respiratory frequency (f) in boys (n=23) aged 5 at rest, during and after treadmill exercise at submaximal and maximal intensity Symbols as in Fig 1

After the end of this submaximal activity the mean values of the parameters recorded dropped at first rapidly thereafter more slowly—probably following an exponential curve— During the five minutes of rest, the starting values were almost restored. Already at the end of the second minute of recovery existing differences between the values of recovery and the values at rest were no more statistically significant. Solely as far as the oxygen uptake is concerned, this was observed only after three minutes of recovery

During the second work load, which was rather a maximal one, all the parameters investigated showed a steep, peak shaped increase. Except for the breathing rate, all values recorded at the first, second and third minute of work were beyond their confidence limits. Thus, the conditions of a steady state were not fulfilled. We could e.g record in nurse apprentices at the same work load, mean maximal values of the heart rate, which—for a mean increase of 81 %—were only few beats/min lower than those of the children of 5 years of age.

Immediately after the end of exercise, a steep decline of the mean values occurred. The values at rest (before the beginning of the second exercise) were not yet attained again after 5 min of recovery However from the 4th min on, the differences showed no statistical significance.

The respiratory equivalent showed a different change pattern, as compared to the other findings. At the beginning of work a diminution of this parameter was observed, whereas after exercise its value increased. This tendency we had already observed in previous investigation. Thus we are in agreement with the findings of other authors who observed this characteristic "break" of the respiratory equivalent in the first phase of the work. This might be due to the fact that at the beginning of the exercise, oxygen uptake increases relatively more rapidly as compared to the air volume ventilated per minute. This is, however, valid only for the submaximal exercise (horizontal run at 4 km/hour)

SUMMARY

1. Treadmill exercise in 5 years old boys and girls showed an initial increase of VO_2 V_T breathing and heart rate, oxygen pulse and pulmonary ventilation. A relative steady state was rapidly attained during submaximal work load. The initial rise of the pulmonary ventilation is realised mainly owing to increase in the breathing rate. During work at maximal intensity both breathing rate and respiratory volume increased, the latter even stronger.

The respiratory equivalent decreased at the beginning of the submaximal exercise and increased during the following recovery time. At maximal work the respiratory equivalent initially dropped and then increased already during work.

Differences were observed between boys and girls groups, which were, however not statistically significant. The mean values of $\dot{V}O_2$ O_2-pulse and $\dot{V}_E$ were higher in boys, whereas girls showed higher values of the heart rate

REFERENCES

1 Klimt, F Mai, G., and Wilhelm, K. Laufbanduntersuchungen im (Klein-)Kindesalter *Dtsch Ges wes 24* 317 1969

(F.K.) Institutes für Infektionskrankheiten im Kindesalter Städt. Klinikum, 1115 Berlin-Buch, Wiltbergstr 50, DDR.

Key words Treadmill exercise 5 years children, oxygen uptake, pulmonary ventilation.

Acta Paediat Scand Suppl 217 1971

INVESTIGATIONS ON THE STANDARDIZATION OF ERGOMETRY IN CHILDREN

F KLIMT and G B. VOIGT

From the I stitut fü Iarf kilonskrankheiten m Kinderalter Städt Klinikum Berlin-Buch, DDR

There is—to a large extent—a lack of data showing the *relationship between the biological capacities* of children on the bicycle ergometer *and the number of revolutions per minute crank length* and *saddle height* This prompted us to carry out such investigations with 182 six eight and ten-years old boys. At the present time we have the findings of 617 individual tests at our disposal.

METHOD

In order to be able to carry out such investi gations even with younger children accessory equipment was developed and constructed (1) for a universal ergometry (Lauckner Berlin-Mariendorf) already on the market. During the application of the ergometric load (2 watt/kg body weight, 6 min in sitting position) ECG heart rate (HR) the sum of heart beats during six periods, the oxygen uptake ($\dot{V}O_2$) the tidal volume (V) and the respiratory rate (RR) were registered, and the respiratory minute volume ($\dot{V}$) the oxygen pulse and the respiratory equivalent (RE) were deter mined after completion of the tests. We also calculated the total sum of heart beats during exercise (TSHB6) the total sum of heart beats during recovery the pulse sum during activity (PSDA6) and the pulse sum during recovery

) These experimental results ere obtained within the framework of research project of the Ministry of Health of the German Democratic Republic designated as Prophylactic Health Measures in Childhood and Youth

The data from the investigations were classified according to age and statistically evaluated (mean values, dispersion, confidence regions and tolerance ranges as well as one- and two-factors analyses of variance)

RESULTS

In all three age groups we were able to establish a good correlation between the biological parameters ascertained in the investigations at different pedal rates. With the aid of multiple t-tests in a one-factor analysis of variance it was possible to verify that the majority of the mean values obtained in these investigations were statistically significant. A significant increase in the biological parameters measured, e.g HR, V V_{O_2} $\dot{V}_E$, total sum of heart beats during work occurred especially when the pedal rate was increased from 50 to 70 r p m. The mean value differences of the mentioned parameters were also significant at pedalling speeds of 50 and 70 r p.m. (Figs 1)

Our next step was to investigate the relationship between the length of the crank (CL) and ef ficiency using ergometric loads at constant speed and with the load selected in relation to body weight. Employing the lowest values obtained for HR, $\dot{V}$ and V_2 as well as the total pulse values during work, we were able to establish an optimum crank length (CL) of 13 cm for 6-years olds. This optimum value, as compared with the CL of 10 and 18 cm, could also be verified statistically by

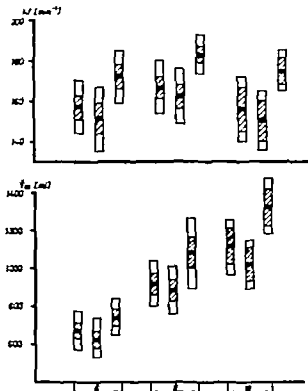


Fig. 1 Heart rate (Hf) and oxygen (VO₂) in boys aged 6, 8 and 10 years during 2 W/kg body weight on bicycle ergometer with three different pedal rates. The columns show mean values with ±SD after 6 min. work at pedal rates 30, 50 and 70 rpm.

means of one factor variance analysis. With a CL of 15 cm the 8-year old boys showed significantly lower HR and TSHB6 values than with CL values of 10 and 20 cm. Within the range of CL including 12, 15 18 and 20 cm, such biological parameters as *HR*, V_E, V_{O_2} *TSHB6* and *PSDA6* in 10-year olds showed a distinct correlation with the tested crank length. Correspondingly the lowest level of their mean values was noted at 15 cm. Especially the total and performance sums of heart beats during 6 periods registered with a crank length of 15 cm were significantly lower than the values measured when using 12 and 20 cm cranks.

The difference in the mean values of HR determined with CL of 15 and 20 cm and also the V_{O_2} with crank lengths of 12 and 15 cm were also significant. For our investigations we have adopted the optimum saddle angle from the findings of Müller (2) Since there is a great difference in the lengths of the legs of children in particular we considered it advisable, however not to indicate the saddle height in cm, but to relate it to the length of legs in order to facilitate comparison. We therefore measured the angle at the knee joint with th pelvis fixed horizontally and the heel resting on the pedal in its lowest position. When the knee joint was extended to the maximum of 180° the children had the tendency to slide to and from the saddle during cycling. The biological data found, such as heart rate, total sum of pulse beats during exercise and pulse sum during activity suggest that the optimum effeciency will be obtained with an average saddle hegth corresponding to a knee joint angle of 15

In individual cycling tests we could also demonstrate the effect of the body bearing on the work capacity on the bicycle ergometer

SUMMARY

1 The biological work capacity of children on the bicycle ergometer is different with the same mechanical work capacity depending on pedal rate, crank length and saddle height.

2. There are too low too high and optimum pedal *rates, crank lengths and saddle height* concerning the economy of working capacity during ergometrical exercise.

3 The following optimum values could be determined during physical load at an intensity of 2 watts/kg body weight Pedal rate—50 r p.m. for the age groups of 6, 8 and 10 years. Saddle height a corresponding knee joint angle of 150 angular degress for the age groups of 6, 8 and years. Crank length 13 cm for the group of 6-years old boys and 15 cm for the group of 8 and 10-years old boys.

REFERENCES

1 Klimt, F Mai and Voigt, G B Ergometerzusatzteile für Kinder-ergometrische Untersuchungen *Pädiat G enzgeb 9* 225, 1970

2. Muller E. A. Der Einfluss der Sattelstellung auf das Arbeitsmaximum und den Wirkungsgrad beim Radfahren *Arbeitsphysiol, 10* 1 1939

(F K) Institut für Infektionskrankheiten im Kindesalter des Städischen Klinikums, 1115 Berlin-Buch, Wiltbergstrasse 50, DDR.

Acta Paediat Scand Suppl 217 1971

PHYSICAL FITNESS OF THE CZECHOSLOVAK 12 AND 15-YEAR-OLD POPULATION

SELIGER, V CERMAK, V HANDZO P HORAK, J JIRKA, Z., MACEK, M., PRIBIL, M., ROUS, J SKRANC, O ULBRICH, J & URBANEK, J.

From the Department of Physiology, Faculty of Physical Education and Sport Charles' University Prague Czechoslovakia

The nature of the organism s reaction to a physical load enables us to evaluate the organism s adaptation. That is why we have been interested in studying this reaction. There are numerous papers in the literature which deal with this subject even in the case of a growing organism.

The great differences among the results (5 13 14) of functional indices measurements presented by various authors may be explained by a number of circumstances.

In this study we evaluated the results of physical fitness examinations carried out by us on youths in two age groups.

METHODS

S lectio f the pop lation sample 11 laboratories, locatedin various parts of our state (19) participated in the investigations

Approximately one half of the subjects were boy and the other girls The investigation was carried out on tw ge groups, on children 12±0 5 and 15±0.5 years of ge The ratio of urban to rural population followed from the type of laboratory

Basic anthropometrical data. W measured body eight and body height by the usual methods. The fat percentage was calculated from ten skinfold thicknesses measured ith caliper The results are listed in Table 1.

Loading the organism by exercise on bicycle ergometer The loading technique followed the instructions for International Biological Programme investigations (2) The initial calming-down period, with the subject sitting on the bicycle ergometer, was followed by three submaximal loads; each lasted 6 minutes and was separated from the others by 1 minut pause. W usually chose the loads according to the system 1.0—1.5—2.0 W/kg body eight; (19) for ery fit individuals it was 1.5— 0—2.5 W/kg. Maximum loading usually began at load hich was 1.0 W/kg greater than the preceding submaximal load and was then increased by 16 W each minute up to the subjects exhaustion which concluded the ride, hich usually lasted 3—5 minutes.

The measured functions In addition other indices (19) w measured the heart rate, pulmonary entilation, oxygen uptake, and carbon dioxide expenditure both at rest and during work At the end of each load expired air was collected in plastic bags. The expired air samples were analyzed in Zeiss interferometer. Heart rates were recorded during the last 15 seconds of each load.

RESULTS AND DISCUSSION

The results of our examinations are listed in Tables 1 and 2 from which following conclusions can be drawn

G owth and d elopm nt As far as the body height and weight are concerned, the boys in both

---

The results of IBP investigations were made in collaboration with 10 other co-working places under responsibility of mentioned scientists On the research programme took part moreover

K Bartak, V Bosák, L Cerny V Drazil, M. Háj ková, V Havel, L Havlíčkova, E Hornák, M Jurásek, J Kvapilík H Lukácová, E Macková, J Machovcová, M Malkovská, J Matejková, V Minarovjech, B. Mrzena, J Novák, V Novotny J Paraková, J Piric, Z Plachetа, A Pribylová, V Sobolová, J Tintera, L. Vaak J Vavra, K. Yaba, V Zelenka, K Zika

Table 1 *Physical characteristics of experimental subjects*

	Boys				Girls			
	12 years		15 years		12 years		15 years	
	mean	S.D	mean	S.D	mean	S.D	mean	S.D
Number	301	–	399	—	294	—	322	
Age (yrs)	11.8	0.27	14.8	0.21	11.8	0.25	14.8	0.20
Weight (kg)	38.6	6.24	55.9	9.21	39.6	6.09	51.4	6.92
Height (cm)	148.1	6.58	168.3	8.54	150.1	6.44	162.7	5.85
Fat (%)	17.3	4.30	13.5	4.03	21.1	3.30	19.1	3.49
W 170	90.6	37.7	148.4	39.5	66.5	23.6	99.0	26.4
W 170/kg BW	2.4	0.8	2.6	0.6	1.7	0.6	1.9	0.4
W 170/kg LBM	2.8	1.0	3.0	0.7	2.1	0.7	2.3	0.4
W 170/m² BSA	71.0	26.9	91.0	23.2	51.2	18.2	63.1	14.8

Table 2 *Functional indices at rest and during work on bicycle ergometer*

	Load W/kg	Boys 12 years mean	S.D	Boys 15 years mean	S.D	Girls 12 years mean	S.D	Girls 15 years mean	S.D.
Watts	1.0	39.0	6.6	58.6	11.7	38.7	6.6	53.3	6.5
	1.5	58.1	9.1	87.9	16.4	57.9	9.5	80.2	11.0
	2.0	77.6	12.1	116.7	21.8	77.0	12.5	107.2	14.6
	max	160.1	27.7	241.7	38.8	141,7	26.4	189.7	27.1
Heart rate, rest		92	14.1	86	15.4	101	15.9	94	12.9
(beats/min)	1.0	1[illegible]8	16.0	116	13.2	145	16.5	135	15.2
	1.5	145	16.9	134	13.4	163	17.0	157	15.1
	2.0	163	17.6	153	14.1	179	15.5	176	14.2
	max	195	10.0	195	8.7	198	10.5	197	8.3
Oxygen uptake	rest	0.26	0.06	0.33	0.07	0.24	0.05	0.28	0.05
(L/min)	1.0	0.77	0.14	0.98	0.20	0.75	0.15	0.88	0.15
	1.5	0.92	0.18	1.25	0.24	0.91	0.16	1.11	0.17
	2.0	1.13	0.19	1.51	0.32	1.08	0.21	1.37	0.22
	max	1.69	0.48	2.57	0.51	1.48	0.29	1.93	0.33
Max. Oxygen uptake/kg		43.8	12.3	46.0	9.7	37.5	7.3	37.6	6.4
		12	3.8	12	4.3	9	3	10	3.2
Ventilation	1.0	4	5.4	27	6.7	22	5	25	5.2
(L/min)	1.5	27	5.9	34	8.4	27	6	32	5.8
	2.0	32	6.9	41	9.7	33	8	41	8.1
	max	59	11.4	106	20.5	53	11	72	13.4

age groups exceed the average somewhat. Similarly in the girls, body height ranged from the average to slightly greater values, body weight being proportional there to.

Oxygen uptake. Oxygen uptake increases linearly with increasing load. The maximum values attained differ according to age and sex. The average values attained appear to be true maximal ones. This follows most obviously from the levelling off attained in both oxygen uptake related to load and heart rate related to oxygen uptake. In girls in both age groups there was no statistically significant difference between the urban and rural population sample but there was in the boys. In comparison

with most data presented in the literature, the absolute values for maximum oxygen uptake, as attained in our experiments, was less. Maximum oxygen uptake values found for boys in both age groups (44 and 46 ml/min kg, respectively) and girls (38 and 38 ml/min kg, respectively) can be compared to those obtained by Knuttgen (9) in larger samples for 15—18-year old boys and girls (50 and 34 ml/min kg, respectively) by Allen (4) for 12 year olds (46 and 38 ml/min kg, respectively) etc. The values for maximum oxygen uptake, as determined by Astrand (6) in smaller samples, prove to be substantially greater a circumstance which may have been caused by great physical fitness of the population involved in the sample.

Pulmonary ventilation Ventilation increases linearly both with increasing load and increasing oxygen uptake, up to a load intensity of about 2 W/kg, as has been stated repeatedly We found no differences between the pulmonary ventilation of the urban and rural population, except for 12 year old urban girls, in whom maximum pulmonary ventilation proved to be greater Even here the maximum values attained in our two age groups (boys 59 and 106 l/min respectively girls 53 and 72 l/min respectively) were lower than data given in the literature, which again becomes most obvious in comparison with Astrand s results (6)

Heart rate The increase in heart rate with increasing load was, on the whole, consistent descriptions hitherto presented in the literature. In girls the maximal values (198 and 197 beats/min respectively) were somewhat higher than in boys (195 and 194 beats/min respectively) These heart rates correspond with data presented in both the Czechoslovak and foreign literature (7 17)

Work capacity at heart at of 170 beats/min (W_{170}) A comparison with various data from the literature (8, 12, 17 20) shows that W_{170} of our population, especially that of the 12 year old, is lower This concerns both absolute representation and values related to body weight or lean body mass. Our values most closely approach those obtained by Howell and McNab (8) in their large Canadian sample. An analysis shows that the explanation is in part to be found in the experimental methods and, in part, in the actual choice of the population sample. Thus, the data given by Rutenfranz (16) which had been attained with continuously increased loads, belong to the highest ever presented in the literature. The experiments by Mocellin and Rutenfranz (12) showed that the difference between continuous and graduated loading amounts to about 12 W As to the sample choice, most authors investigate small samples, usually examining volunteers, and practise no selection at all. Thus, participants in experiments are physically fit children, who are well motivated in advance by their own interest. On the contrary the selection of greater ensembles with at least some degree of randomness should provide better information on the population sample. Such a selection would provide a truly representative sample, even in respect to anthropometrical indices such as body weight, somatotype, body fat percentage, emotional state, general attitude to the experiments, motivation for a true maximum performance, etc. For these reasons the results obtained in our sample were in relatively good agreement with the Canadian results (8) especially in respect to the 12 year olds.

Our values of W_{170} (in the 12 and 15-year old children they were respectively 91 and 148 W in boys, 67 and 99 W in girls) show that the girls reach about 2/3 to 3/4 of the work capacity of the boys of similar age. Our data on W_{170} corresponds with observations made in children by Rutenfranz (16) Howell and McNab (8) and in adults by McNab et al. (10) Bengtsson (7) on the contrary did not find any differences in W_{170} until 15 years of age. Similar results appear when the afore mentioned values are related to body weight or lean body mass. In our sample W_{170}/kg increased with age by about 10 % in contradiction to several results by other authors (1 8, 17) according to whom there is either no increase at all or sometimes even a decrease from 12 to 15 years of age. What is quite striking is the lack of agreement with observations made in a large sample by the Canadian authors (8) who found that W_{170} decreases from 13 years of age in girls. Our boys displayed the same average value (148 W) W_{170}

reported by Allard and Goulet (3) for a larger sample of physically untrained adult Canadians (149 W for 101 persons) Thus, our population proved to be relatively fit.

Physical training causes a relatively rapid improvement in both cardiovascular fitness and general endurance, in consequence of which W_{170} also increases (1 15 18) When the influence of physical development is excluded, i.e when the particular data are related to body weight, (20) can serve as the index of physical fitness (20) When evaluated from this point of view the samples of a smaller population belong, according to the classification by Soulek (20) to a group that lies between youth of average adaptation engaging in multilateral exercise and youth engaging in special sports activities. This can be explained by the relatively high degree of the physical activity of individuals, as reported anamnestically and the rather large percentage of sports competitors to be found especially among 15 year old population.

In all groups and both sexes of the population studied the W_{170} correlates positively (at the level of significance $p=0.01$) with body weight, height, maximum oxygen uptake and oxygen pulse and negatively with the maximum heart rate. For W_{170} related to body weight, lean body mass and body surface area, the correlations failed to result in any congruence for all groups of the population examined there was practically no correlation with body weight and body height while there was still correlation with maximum heart rate. Correlation with oxygen uptake and oxygen pulse was not always been found. These findings of ours are in good agreement with those presented in the literature (7 8, 21)

SUMMARY

We examined the 12 and 15-year old youths, 301 and 399 boys respectively and 294 and 322 girls respectively who exercised on a bicycle ergometer with graduated workloads up to the maximum. In 11 laboratories, the persons to be examined were selected in two ways. The schools were selected randomly from those located within a range of 30 km from each laboratory At these schools all individuals belonging to the appropriate age group were examined. A loading of 1.0—1 5 —2.0 W/kg body weight proved appropriate. For a number of indices, lower values were found than reported in the literature. Maximum oxygen uptake in the two age groups reached 44 and 46 ml/min kg, respectively in boys and 38 and 38 ml/min kg, respectively in girls. Similarly maximum pulmonary ventilation was 59 and 106 l/min respectively in boys and 53 and 72 l/min respectively in girls. Maximum heart rate amounted to 195 and 195 beats/min respectively in boys and 198 and 197 beats/min in girls. The work capacity at 170 beats/min reached 91 and 148 W respectively in the boys and 67 and 99 W respectively in the girls. The origin of different findings presented in the literature are discussed.

REFERENCES

1 Andersen, K. L and Nagel, J R. Physiological adaption to high level of habitual physical activity during adolescence. *Int Z A gew Physiol, 28* 209 1970.

2 Astrand, P O Experimental studies of physical working capacity in relation to sex and age Copenhagen, 1952

3 Astrand, P O Engström, L., Eriksson, B O Karlberg, P Nylander I Saltin, B. and Thorén, C Girl swimmers. *Acta Paediat Scand* Suppl 147 1963

4. Faulkner, J A. Physiology of swimming and diving. *I* H B Falls (ed) *Exercise physiology* New York, 1968

5 Fetter V Prokopec, M Suchy J and Titlbachová, S *Anthropology* (Czech) Praha, 1967

6 Havel, V and Skranc, O Oxygen working capacity of 15 to 17 years old swimmers (Czech) *Cs Fysiol 13* 205 1964

7 Howell, M Z and MacNab, R B. The physical work capacity of Canadian children aged 7 to 17 *Canad As Health Phy Educ Recreation* 1968.

8. Mácek, M and Skranc, O Physical fitness of Czechoslovak children at 12 and 15 years of age—ergometrical examinations *Acta Univ Carol Gym* 5 48, 1970

9 Nagel, J R and Faulkner J A Maximum oxygen uptakes of college swimmers. *J Appl Physiol 22* 929 1967

10. Nagel, J. R. and Andersen, K. L. Pulmonary diffusing capacity and cardiac output in young trained Norwegian swimmers, and untrained subjects. *Med. Sci. Sport* *1*: 151, 1969.

11. Mocellin, R. and Rutenfranz, J. Methodische Untersuchungen zur Bestimmung der Körperlichen Leistungsfähigkeit (W170) im Kindesalter. *Z. Kinderheilk.* *108*: 61, 1970.

12. Pařízková, J. The development of active body mass and fat in children and adolescents (Czech). *Thomayerova sbírka* No. 413, Praha, 1962.

13. Seliger, V. and Wagner, J. Evaluation of heart rate changes during exercise on bicycle ergometer. *Physiol. bohemoslov.* *18*: 41, 1969.

14. Seliger, V. Physical fitness of Czechoslovak children at 12 and 15 years of age—working methods. *Acta Univ. Carol. Gymn.* *5*: 10, 1970.

15. Soulek, V. Rating of the values PWC170 (Czech). *Teor. Praxe Těl. Vých.* *17*: 622, 1969.

16. Szabó, S. Die Zunahme des Herzvolumens und Leistungsfähigkeit als Folge eines regelmässigen Trainings bei Schwimmern im Pubertätsalter. *Med. Sport*, *9*: 280, 1969.

19. Vávra, J. Physical fitness of Czechoslovak children at 12 and 15 years of age—spirometrical examinations. *Acta Univ. Carol. Gymn.* *2*: 70, 1970.

(V.S.) Department of Physiology
Faculty of Physical Education and Sports
Ujezd 450, Praha
Czechoslovakia

Key words: Swim training, boys 15—19 years, submaximal and maximal work loads, oxygen uptake, work capacity, pulmonary ventilation, body composition

reported by Allard and Goulet (3) for a larger sample of physically untrained adult Canadians (149 W for 101 persons) Thus, our population proved to be relatively fit.

Physical training causes a relatively rapid improvement in both cardiovascular fitness and general endurance, in consequence of which W_{170} also increases (1 15 18) When the influence of physical development is excluded, i.e. when the particular data are related to body weight, (20) can serve as the index of physical fitness (20) When evaluated from this point of view the samples of a smaller population belong, according to the classification by Soulek (20) to a group that lies between youth of average adaptation engaging in multilateral exercise and youth engaging in special sports activities. This can be explained by the relatively high degree of the physical activity of individuals, as reported anamnestically and the rather large percentage of sports competitors to be found especially among 15-year old population.

In all groups and both sexes of the population studied the W_{170} correlates positively (at the level of significance $p = 0.01$) with body weight, height, maximum oxygen uptake and oxygen pulse and negatively with the maximum heart rate. For W_{170} related to body weight, lean body mass and body surface area, the correlations failed to result in any congruence for all groups of the population examined there was practically no correlation with body weight and body height while there was still correlation with maximum heart rate. Correlation with oxygen uptake and oxygen pulse was not always been found. These findings of ours are in good agreement with those presented in the literature (7 8, 21)

SUMMARY

We examined the 12 and 15-year old youths, 301 and 399 boys respectively and 294 and 322 girls respectively who exercised on a bicycle ergometer with graduated workloads up to the maximum. In 11 laboratories, the persons to be examined were selected in two ways. The schools were selected randomly from those located within a range of 30 km from each laboratory At these schools all individuals belonging to the appropri[ate] age group were examined. A loading of 1 0—[…] —2.0 W/kg body weight proved appropriate. [In] a number of indices, lower values were found th[an] reported in the literature. Maximum oxygen upt[ake] in the two age groups reached 44 and 46 ml/m[in] kg, respectively in boys and 38 and 38 ml/min [kg] respectively in girls. Similarly maximum pulmo[n]ary ventilation was 59 and 106 l/min respectiv[ely] in boys and 53 and 7_ l/min respectively in gi[rls]. Maximum heart rate amounted to 195 and 1[…] beats/min respectively in boys and 198 and 1[…] beats/min in girls. The work capacity at 170 bea[ts/]min reached 91 and 148 W respectively in the bo[ys] and 67 and 99 W respectively in the girls. T[he] origin of different findings presented in the [li]terature are discussed.

REFERENCES

1 Andersen, K. L., and Nagel, J R. Physiologi[cal] adaption to high level of habitual physical [act]ivity during adolescence. *Int Z Angew Physiol, 28* [...] 1970.

2 Astrand, P O Experimental studies of physical working capacity in relation to sex and age. C[o]penhagen, 1952.

3 Astrand, P O Engström, L., Eriksson, B O Ka[rl]berg, P Nylander, I., Saltin, B and Thorén, C Girl swimmers. *Acta Paediat Scand* Suppl. 14[…] 1963

4 Faulkner, J A. Physiology of swimming a[nd] diving *I* H. B. Falls (ed.) *Exercise physiology* New York, 1968.

5 Fetter V Prokopec, M Suchy J and Titlbachov[á] S *Anthropology* (Czech) Praha, 1967

6 Havel, V and Skranc, O Oxygen working capaci[ty] of 15 to 17 years old swimmers (Czech) *Cs Fysiol* *13* 205, 1964.

7 Howell, M. Z. and MacNab, R. B. The physical work capacity of Canadian children aged 7 to 1[…] *Canad Ass Health Phys Ed Recreation* 1968.

8 Macek, M and Skranc, O Physical fitness [of] Czechoslovak children at 12 and 15 years of age—ergometrical examinations *Acta Univ Carol Gymn* 5 48, 1970.

9 Nagel, J R. and Faulkner, J A Maximum oxyge[n] uptakes of college swimmers. *J Appl Physiol 22* 979 1967

Table 1 Averaged results for oxygen consumption (STPD), pulmonary ventilation (BTPS) and heart rate in steady state during work with concentric and with eccentric muscle contractions

Power W	Velocity rpm	Averaged Results W_{con}			Averaged Results W_{ecc}		
		V_{O_2} l/min	V_E l/min	HR beats/min	V_{O_2} l/min	V_E l/min	HR beats/min
0	20	0.34	7.3	66	—	—	—
0	60	0.48	11.6	70	—	—	—
0	100	1.03	23.2	96	—	—	—
15	20	0.50	10.5	70	0.35	9.6	64
15	60	0.62	12.7	77	0.36	10.2	64
15	100	1.18	26,0	97			
30	20	0.86	16.7	95	0.38	9.6	68
30	60	0.77	16.1	86	0.38	10.7	68
30	70	—	—	—	0.41	10.6	72
30	100	1.40	31.2	111	—	—	—
55	20	1.13	22.3	98	0.54	11.9	80
55	60	1.00	19.4	90	0.40	9.7	73
55	100	1.53	35.3	113	0.67	18.6	83
80	20	1.66	33.6	122	0.58	14.5	82
80	60	1.34	26.5	105	0.43	12.4	76
80	100	1.78	42.0	122	0.65	17.8	83
105	20	2.32	60.1	144	0.80	18.2	88
130	40	—	—	—	0.73	18.2	86
130	60	2.00	41.8	132	0.54	15.4	78
130	100	2.38	62.2	146	0.72	18.4	92

ranging from 15—130 Watt and at speeds ranging from 20—100 rpm (revolutions per min). After 7 min of exercise, expired gas was collected in Douglas bags and analyzed according to Scholander (15). Heart rate was determined during the collection period by palpation.

The averaged results for oxygen consumption, pulmonary ventilation, and heart rate for the two subjects are presented in Table 1 and the average results for oxygen consumption are also plotted vs work intensity in Figures 1. There is an increased oxygen consumption with increasing intensity of work in both W_{con} and W_{ecc}, although the increases were far greater in W_{con}. In both types of exercise, the oxygen cost was also affected by the rate of pedaling. If the oxygen cost of free wheeling cycling activity employing concentric contractions was employed as a baseline, the net efficiency could be calculated from the inclination of the V_{O_2}/work intensity relationship. Employing this method, the mechanical efficiency was greatest at the fastest speed (100 rpm) and lowest at the slowest speed (20 rpm).

When the heart rates were compared to oxygen consumption it could be observed that the heart rates in W_{ecc} exceeded to a small extent those obtained in W_{con} at similar oxygen uptakes. For the most part, however, the relationship was quite consistent with a higher heart rate corresponding to a higher oxygen consumption. The type of activity had small influence and pedal frequency had little or no influence on this relationship.

A hyperventilation was observed when W_{ecc} was compared to W_{con}. During W_{ecc}, the ventilatory equivalent was higher during work at 100 rpm than at the other frequencies. The hyperventilation evidenced no consistent trend as far as work capacity or rpm were concerned.

Training with W_{ecc} and oxygen consumption. The effect of 3—5 weeks training with W_{ecc} at high work intensities and, therefore, high muscle tensions was studied in three subjects (7). W_{ecc}

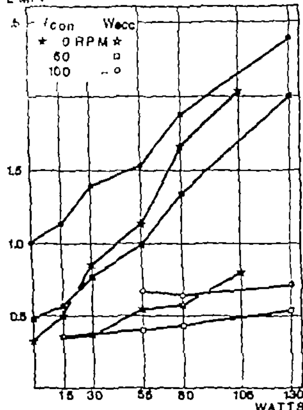


Fig 1 Relationship of steady state oxygen consumption to work performed with concentric and eccentric muscle contractions at various frequencies. Plotted points represent means of 2 subjects.



Fig 2 Effect of training with eccentric contractions (5 Nov and 7 Nov) and detraining (10 Apr) upon oxygen uptake during extended bouts of W_{ecc}. Results of 3 selected experiments are presented. Work intensity = 10 W

was performed as cycling downhill on an inclined treadmill. Expired gas was collected in Douglas bags during various phases of the exercise period and analyzed according to Scholander (1947). Heart rate was monitored by palpation.

The results of training and, afterwards, detraining on oxygen consumption during extended bouts of W_{ecc} are shown in Figure (selected experiments) for one subject (H). The term detraining is employed to describe the 4-month period following the training experiments during which time the subject engaged in no W_{ecc} activity resembling the training sessions. The results of the experiments of the two other subjects followed the same pattern. Typical of the oxygen consumption response during extended bouts of W_{ecc} is the experiment of November 5th. A steady increase in oxygen consumption was observed which greatly exceeded any such increases seen in W_{con}. The increase in $\dot{V}_{O_2}$ from the 9th min to the 23rd min was 230 ml/min or a 19 % increase. After additional training, the oxygen consumption became lower throughout the entire work period but, even more dramatic, was the disappearance of the tendency toward large increase.

Four possible explanations have been advanced which could cause or contribute to the disappearance of the large increase in oxygen consumption with training (7) the conditioning of those muscle fiber types better suited to aerobic energy release, changes in the motor pattern employed in the cycling, adaptive changes in the crossbridging mechanism between muscle filaments, and changes in the manner in which energy was received by the muscles from the bicycles. The most intriguing of the possibilities is, perhaps, the latter If the muscle cells were able to utilize the energy either in the biochemical processes (such as high-energy phosphate resynthesis) or directly in the tension-producing events, this would spare aerobically released energy and oxygen consumption. If the cells were less able to continue this transfer throughout the early experiments, a slow rise in oxygen consumption would have to occur as the aerobic processes took over An additional observation was that the increase in oxygen consumption in the experiment of 5 Nov amounted to an energy release of 2.6 kcal/min (employing 4.9 kcal/l O_2) The caloric

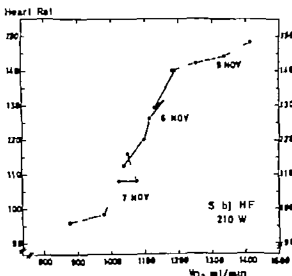


Fig. 3 Relationship of heart rate to oxygen consumption for 3 selected training experiments in W_{ecc} for subject HF First determinations began approximately 3 min after initiation of work and are indicated by open circles. Work intensity=210 W

equivalent of the energy being received from the bicycle amounted to 3 0 kcal/min. In each subject, the energy delivered by aerobic processes decreased by an amount within and approximating the energy available from the bicycle as a result of training. Whatever the changes which occurred might have been, they were not long lasting when training was terminated. As can be seen with the experiment of 10 April, the oxygen consumption response resembled that of the pre-training state.

In all of the experiments, heart rate closely followed oxygen consumption. In experiments where both elevations and depressions in oxygen consumption were observed, heart rate showed similar directions of change. The relationship of heart rate to oxygen consumption for 3 training experiments with subject HF are presented in Figure 3.

Oxygen debt in W_{con} and W_{ecc}. A comparison of oxygen uptake responses throughout 3-min and 6-min bouts of exercise and during recovery in W_{con} and W_{ecc} was made employing four human subjects (8) The method of exercise was cycling on an inclined treadmill at work intensities equated by the elicited oxygen uptake responses (approximately 1 l/min) The work intensities employed were 3 to 5 times greater in W_{ecc} than in W_{con}. A small but consistent deficit, averaging 262 ml, was seen in the W_{con} experiments but little or no deficit in W_{ecc}. Three of four subjects evidenced no deficit in W_{ecc}. The debts following W_{con} exceeded the deficits in both the 3-min and 6-min experiments, averaging 1 090 ±60 ml and 1 143 ±56 ml, respectively Following work for 3 and 6 min in W_{ecc}, the debts averaged 1 035 ±55 ml and 809 ±65 ml, respectively There was, therefore, a tendency for oxygen debt to increase with work time in W_{con} and to decrease with work time in W_{ecc}. The tendency for a reduction in oxygen debt could constitute a further indication of the possibility that muscle cells can utilize the energy received from the ergometer during W_{ecc}. While there was a definite tendency toward higher heart rates and greater pulmonary ventilation in W_{ecc} at similar oxygen consumption levels as W_{con}, both parameters corresponded quite closely to oxygen consumption. Estimations of muscle blood flow (^{133}Xe clearence) showed no significant difference between the two types of work in spite of the vastly different tensions involved.

Summary Physical exercise involving eccentric contractions presents vastly different physiological responsesthan exercise with concentric contractions, which is the form usually studied. In order to produce the same tensions, the muscles utilize a much smaller volume of oxygen in W_{ecc} and the accompanying circulatory and pulmonary reactions are correspondingly smaller Another way of describing the relationship is that, at the same levels of oxygen consumption and circulatory and pulmonary stress, the body is capable of producing much higher muscle tensions (and for extended periods of time) Evidence is also observed which supports work with isolated frog muscle that the muscles are able to receive and utilize energy in the contraction processes.

These observations bear careful consideration for

a. the basic study of energetics of muscle contraction.

EXERCISE STUDIES IN CHILDREN USING THE INDIRECT (CO_2) FICK METHOD

C. T. M. DAVIES and S. GODFREY

From the Environmental Physiology Unit Medical Research Council, London School of Hygiene and Tropical Medicine
and
The Institute of Disease of the Chest London, England

Standard methods for measuring cardiac output usually involve right heart catheterisation, dye dilution or inert gas methods. The first two are rarely acceptable in normal children and the last is of little value in disease. Techniques involving arterial sampling or cardiac catheterisation are especially difficult to use during exercise and seriously distressed children. For these reasons we have explored the use of the Indirect (CO_2) Fick Principle for measuring cardiac output in a large group of normal children (Godfrey and Davies, 1970). Subsequently the method has also been applied to several series of children with lung or heart disease.

In the present study 117 subjects aged 6 to 16 performed steady state exercise seated on a stationary bicycle ergometer at one-third and two-thirds of their previously determined maximum working capacity. At each work level a continuous record of cardiac frequency, ventilation and expired gas was monitored until all values were steady. Expired gas was then collected over 1 minute and analysed for CO_2 and O_2. Arterialised ear lobe blood was taken by the method of Godfrey, Wozniak, Courtenay Evans and Samuels (1970) and the mixed venous P_{CO_2} was then measured by a rebreathing method using CO_2 in O_2 mixtures (Jones, Campbell, Mc Hardy, Higgs and Clode, 1967). No downstream correction was applied to the plateau value following the work of Dennison, Edwards, Jones and Pope (1969). The next work load was then commenced.

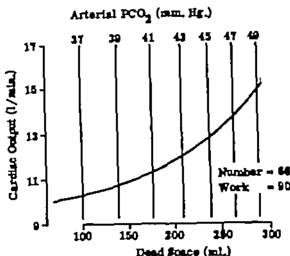


Fig. 1. Example of graph relating all possible simultaneous solutions of the Fick equation for cardiac output and the Bohr equation for dead space over a wide range of theoretical values of P_{CO_2}

A digital computer program (Godfrey 1970) was used to process the results and construct a graph for each work load in each subject relating all possible simultaneous solutions of the Fick equation for cardiac output and the Bohr equation for dead space given by selecting a wide range of theoretical values for arterial P_{CO} (Fig. 1).

Using the plots obtained for each subject we calculated the value for VD and $\dot{Q}$ based on several different estimates of P_{aco_2} such as end-tidal P_{CO_2} and ear blood P_{co_2}. We found that the best esti- of VD was usually given by using end-tidal P_{CO_2}

b. the ergometry employed in exercise physiology research.

c. rehabilitation work, as regards motor learning and strength development.

REFERENCES

1. Abbott, B. C. & Bigland, B.: The effects of force and speed changes on the rate of O_2 consumption during negative work. *J Physiol (London)* 120: 319 1953.
2. Abbott, B. C., Bigland, B. & Ritchie, J. M.: The physiological cost of negative work. *J Physiol (London)* 117: 380, 1952.
3. Asmussen, E.: Positive and negative muscular work. *Acta Physiol Scand 28:* 364, 1952.
4. Asmussen, E.: Experiments on positive and negative work. The Ergonomics Research Society: *Symposium on Fatigue.* H. K. Lewis and Co, London, 1953.
5. Chauveau, A.: La loi de l'equivalence dans les transformations de la force chez les animaux. *C R Acad Sci (Paris)* 122: 113, 1896.
6. Kamon, E.: Negative and positive work in climbing laddermill. *J Appl Physiol,* 29: 1, 1970.
7. Knuttgen, H. G. & Klausen, K.: Effect of training on oxygen consumption in exercise involving eccentric muscle contractions. In press, *Acta Physiol Scand* (Submitted for publication)
8. Knuttgen, H. G. & Klausen, K. Oxygen debt in short-term exercise with concentric acid and eccentric muscle contractions. In press, *J Appl Physiol.* (Submitted for publication)
9. Knuttgen, H. G. Bonde Petersen, F. & Klausen, K. Oxygen uptake and heart rate responses to exercise performed with concentric and eccentric muscle contractions. *Med Sci in Sports* 3: 1 1971.
10. Lichtneckert, S. A. J. Thomson, D. A. & Åkerson, S. L. A reversible ergometer. *Scand J Clin Lab Invest* 23: 373, 1969
11. Müller, E. A.: Ein neues ergometrisches Verfahren *Arbeitsphysiol* 11: 372, 1941
12. Müller E. A.: Energieumsatz und Pulsfrequenz bei negativer Muskelarbeit. *Arbeitsphysiol, 15:* 196, 1953.
13. Nielsen, B. Heat production and heat transfer in negative work. J. D. Hardy (ed.) *In Physiological and behavioral temperature regulation.* In press.
14. Petersen, F. B. A bicycle ergometer for investigating the effect of eccentric exercise with arms and legs. *Int Z Angew Physiol* 27: 133 1969
15. Scholander P. F. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. *J Biol Chem* 167: 235 1947
16. Thomson, D. Cardiac output during positive and negative work (Abstract) *Acta Physiol Scand* 1969 Suppl. 330.

(H. G. K.) Boston University—Biology
2 Cummington St.
Boston, Mass. 02215 U.S.A.

Key words: Exercise, eccentric and concentric muscular contractions.

Acta Paediat Scand Suppl 17 1971

EXERCISE STUDIES IN CHILDREN USING THE INDIRECT (CO_2) FICK METHOD

C. T. M. DAVIES and S. GODFREY

From the Environmental Physiology Unit, Medical Research Council, London School of Hygiene and Tropical Medicine
and
The Institute of Diseases of the Chest London England

Standard methods for measuring cardiac output usually involve right heart catheterisation, dye dilution or inert gas methods. The first two are rarely acceptable in normal children and the last is of little value in disease. Techniques involving arterial sampling or cardiac catheterisation are especially difficult to use during exercise and seriously distressed children. For these reasons we have explored the use of the Indirect (CO_2) Fick Principle for measuring cardiac output in a large group of normal children (Godfrey and Davies, 1970) Subsequently the method has also been applied to several series of children with lung or heart disease.

In the present study 117 subjects aged 6 to 16 performed steady state exercise seated on a stationary bicycle ergometer at one-third and two-thirds of their previously determined maximum working capacity At each work level a continuous record of cardiac frequency ventilation and expired gas was monitored until all values were steady Expired gas was then collected over 1 minute and analysed for CO_2 and O_2. Arterialised ear lobe blood was taken by the method of Godfrey Wozniak, Courtenay Evans and Samuels (1970) and the mixed venous P_{CO_2} was then measured by a rebreathing method using CO_2 in O_2 mixtures (Jones, Campbell, Mc Hardy Higgs and Clode, 1967) No downstream correction was applied to the plateau value following the work of Dennison, Edwards, Jones and Pope (1969) The next work load was then commenced.

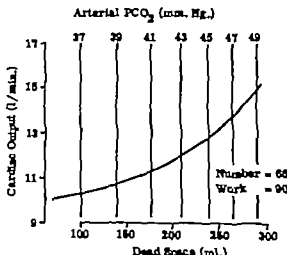
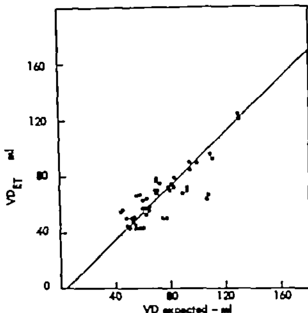


Fig 1 Example of graph relating all possible simultaneous solutions of the Fick equation for cardiac output and the Bohr equation for dead space over a wide range of theoretical values of P_{CO_2}

A digital computer program (Godfrey 1970) was used to process the results and construct a graph for each work load in each subject relating all possible simultaneous solutions of the Fick equation for cardiac output and the Bohr equation for dead space given by selecting a wide range of theoretical values for arterial P_{CO_2} (Fig. 1)

Using the plots obtained for each subject we calculated the value for VD and $\dot{Q}$ based on several different estimates of $P_{a_{CO_2}}$ such as end-tidal P_{CO_2} and ear blood P_{CO_2}. We found that the best estimate of VD was usually given by using end-tidal P_{CO_2}



F g 2. VD estimated from end-tidal P_{CO_2} at rest compared with the expected alues based on body size (Radford, 1954)

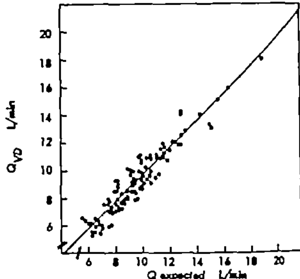


Fig. 3 Q̇ calculated using method ( ) to estimate P_{aCO_2} compared with the expected Q̇ during exercise (from the data of Bevegård et al., 1960)

when we compared the calculated values with the expected values based on body size (Radford, 1954) The correlation with expected VD was best t rest (Fig. 2)

The main object of the project was to obtain *timates of cardiac output and* 3 *alternative values* of P_{CO_2} were used for this purpose —

(a) end-tidal P_{CO_2}
(b) ear lobe P_{CO_2}
(c) the arterial (=alveolar) P_{CO_2} calculated from the Bohr equation needed to give a normal VD predicted from weight and tidal volume.

It was found that there was a highly significant correlation between the Q̇ calculated by all three methods with that predicted for the oxygen con sumption from the adult data of Bevegård, Holmgren and Jonsson, (1960) The best correlation of all ($r = \cdot 94$, $p = < .0005$ $n = 182$) was obtained using method (c) and the results of this study are shown in Fig. 3. We noted that some of our smaller children tended to have cardiac outputs lower than the *corresponding* adult values, but the *differences* were small. We found it impossible to use the method reliably at rest where the veno-arterial P_{CO_2} difference is so small (6—8 mm.Hg.) compared with the difference on exercise (20 to 30 mm.Hg)

SUMMARY

The Indirect (CO_2) Fick method for calculating cardiac output *is easily* applied to young children and gives very reasonable results.[1] In the child with normal lungs it is not necessary to take ar terial or ear lobe blood since the arterial P_{CO_2} may be calculated using an assummed normal dead space.

REFERENCES

Bevegård, S., Holmgren, A. and Jonsson, B. *Acta Physiol Scand*, 49. 279 1960.

Godfrey S. *Respiration* 1970. In press.

Godfrey S. and Davies, C. T. M. *Clin Sci* 39 529 1970.

Godfrey S., Wozniak, E., Courtenay Evans, R. and Samuels, C. S. *Brit J Dis Chest* 1970. In press.

Jones, N. L., Campbell, E. J. M., McHardy G. J. R., Higgs, B. E. and Clode, M. *Clin Sc* 32. 311, 1967

Radford, E. P *J Appl Physiol* 7 451, 1954

(C D) Environmental Physiology Unit
London School of Hygiene
Keppel Street, W C.1 London, England

[1] A more comprehensiv account of these experiments is given elsewhere (Godfrey and Davies, 1970) and the reader is referred to this publication for further infor mation.

CARDIAC OUTPUT DETERMINATION IN EXERCISING CHILDREN—METHODOLOGY AND FEASIBILITY

ODED BAR-OR and ROY J SHEPARD

F m Laboratory for H man Performance Re earch
Institute for Science and Engineering
The P nn yl ania State Uni ersity Uni ersity Park U S A, and
Departm nt of Physiological Hygiene, School f Hygiene
Uni ersity of Toronto Canada

One of the objectives of the International Biological Programme-Human Adaptability Section, has been the determination of cardiac output ($\dot{Q}$) at graded exercise loads in selected populations. A standardized methodology is of obvious importance to such a project planned for laboratories which differ in their degree of sophistication and which study populations of diverse backgrounds.

The population of preadolescents is a case in point Both methods commonly used for Q deter mination, namely direct Fick and dye-dilution, re quire catheterization and arterial puncture and therefore will not be readily accepted by a pre alodescent volunteer

The CO_2 rebreathing technique s "bloodless causes minimal inco enience to the subject and therefore may be suitable for use with children. A number of studies on young adults ha e shown this technique to be valid and reliable compared with more direct methods, (4, 10 11)

A previous report from our laboratories (3) described the circulatory responses to exercise of 10—13 year old children, as measured by the CO_2 re breathing method The purpose of the present report is to discuss some methodological aspects of this technique, with special emphasis on modific ations of the procedure commonly used with adults. In addition, the feasibility of this method for child testing is discussed in some detail.

This investigation as partially supported by PHS Grant No AM 08311 from the National Institute of Arthritis and Metabolic Diseases, by research grants from the Directorate of Fitness and Amateur Sport, Ottawa, and by the Ontario Heart Foundation

MATERIAL

$\dot{Q}$ determinations were made on 29 girls and 27 boys, 10—13 years old. They were all healthy and represented a sample of Metropolitan Toronto school children. Recruiting and randomizing proce dures, as well as body characteristics of the child ren, ha e been described elsewhere (3, 13)

METHOD AND DISCUSSION

Although all children acquired previous ex perience with the use of the nose clip mouthpiece and breathing valve while walking on the treadmill, none of them had any experience with the bicycle ergometer or with the rebreathing procedure Before the test started, some 10 minutes were spent with each child on practicing these proce dures. Special attention was paid to an even re breathing pattern with adequate emptying of the bag. Tidal olume (V) was estimated during this practice and ser ed as a guide to the volume of gas mixture (5 % CO_2, 95 % O_2) to be put into the rebreathing bag.

Fortyeight of the children performed a two-stage uninterrupted bicycle ride at about 50 % and 70 % of their maximal O_2 consumption ($\dot{V}$ $_2$

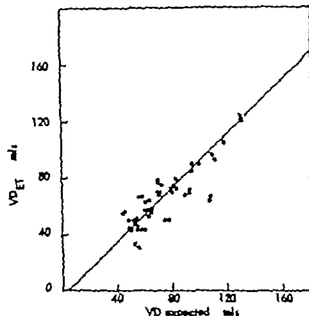


Fig 2. VD estimated from end-tidal P_{CO_2} at rest compared with the expected values based on body size (Radford, 1954)

when we compared the calculated values with the expected values based on body size (Radford, 1954) The correlation with expected VD was best at rest (*Fig.* 2)

The main object of the project was to obtain estimates of cardiac output and 3 alternative values of P_{CO_2} were used for this purpose —

(a) end tidal P_{CO_2}

(b) ear lobe P_{CO_2}

(c) the arterial (=alveolar) P_{CO_2} calculated from the Bohr equation needed to give a normal VD predicted from weight and tidal volume.

It was found that there was a highly significant correlation between the $\dot{Q}$ calculated by all three methods with that predicted for the oxygen consumption from the adult data of Bevegård, Holmgren and Jonsson, (1960) The best correlation of all ($r = .94$, $p = < .0005$ $n = 182$) was obtained using method (c) and the results of this study are shown in Fig. 3 We noted that some of our smaller children tended to have cardiac outputs lower than the corresponding adult values, but the differences were small. We found it impossible to use the method reliably at rest where the veno-arterial P_{CO_2}

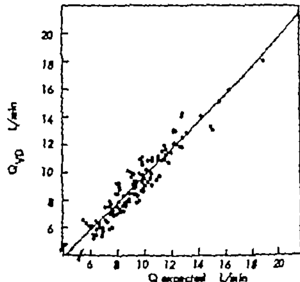


Fig. 3 Q calculated using method (c) to estimate P_{aCO_2} compared with the expected $\dot{Q}$ during exercise (from the data of Bevegård et al 1960)

difference is so small (6—8 mm.Hg.) compared with the difference on exercise (?0 to 30 mm.Hg)

SUMMARY

The Indirect (CO_2) Fick method for calculating cardiac output is easily applied to young children and gives very reasonable results.[1] In the child with normal lungs it is not necessary to take arterial or ear lobe blood since the arterial P_{CO_2} may be calculated using an assummed normal dead space

REFERENCES

Bevegård, S., Holmgren, A. and Jonsson, B. *Acta Physiol Scand* 49: 279 1960.

Godfrey S. *Respiration* 1970. In press.

Godfrey S. and Davies, C. T. M. *Clin Sc* 39 529 1970.

Godfrey S., Wozniak, E. Courtenay Evans, R. and Samuels, C. S. *Brit J Dis Chest* 1970. In press.

Jones, N. L., Campbell, E. J. M., McHardy G. J. R., Higgs, B. E. and Clode, M. *Clin Sci* 32. 311 1967

Radford, E. P *J Appl Physiol* 7 451 1954.

(C.D.) Environmental Physiology Unit
London School of Hygiene
Keppel Street, W.C.1 London, England

[1] A more comprehensive account of these experiments is given elsewhere (Godfrey and Davies, 1970) and the reader is referred to this publication for further information

Table 1 Age [illegible] and [illegible] (in yrs) and [illegible] found

		boys	girls
Number		4	7*
Age, yrs		11.5	11.6
Work load	1st	3	5
	2nd	1	3
	3rd	0	0

One girl had two indequate rebreathing curves

par curves was not related to a special state of fatigue. In fact, most of such curves appeared during the lowest work load. There was no difference between the age of those having inadequate curves and that of the whole test group. It is of interest to note that some 25 % of all the girls had one or more sub-par curves. The corresponding percentage for the boys was 15 %. Numbers are too small to draw a final conclusion from this finding.

The number of usable records would probably have increased still further had time permitted more than 10—12 minutes practice of the test procedure.

DETERMINATION OF ARTERIAL P_{CO} (Pa_{CO_2})

Some authors (4, 7) calculated the exercise Pa_{CO_2} from Bohr's equation, using the Asmussen-Nielsen graph (2) for determination of physiological dead space (V). Others (5, 9) measured the alveolar P_{CO_2} (PA_{CO_2}) by the end-tidal method and used this measurement as representing Pa_{CO_2} with or without correction for a-A gradients. In our previous publication (3) the advantage of using the end-tidal method over the "Bohr Asmussen-Nielsen" method has been demonstrated for children. The conclusion then was that apparently the V_D/V relationship demonstrated by Asmussen and Nielsen, was not valid for children. It was therefore tried to construct a new V_D/V graph for the test group by the use of Pa_{CO_2} values from arterialized capillary blood of a subgroup of the children. Blood was taken from the finger, simultaneously with the $\dot{Q}$ determination, at various

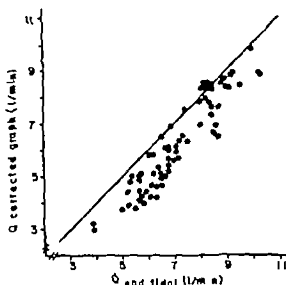


Fig. 2. Comparison between cardiac output ($\dot{Q}$) values obtained by two methods for calculating arterial P_{CO_2}: 1) end-tidal P_{CO_2}, assuming P end tidal CO_2 = PA_{CO_2}. 2) Bohr equation, using corrected V_D/V_T graph.

work loads. Pa_{CO_2} was determined with the Astrup microelectrode. These Pa_{CO_2} values were put in the Bohr equation (assuming $Pa_{CO_2} = PA_{CO_2}$) and V_D thus calculated. The new regression of V_D on V_T was $V_D = (V_T)\ 0.285—64$ (13). The following stage was to calculate $\dot{Q}$ for all the subjects at all work levels by the use of this "corrected" graph. As shown in Fig 2, $\dot{Q}_{corrected\ graph}$ values are about 1 liter/min lower than those obtained by the end-tidal method. This is a result of higher Pa_{CO_2} (about 3 mmHg) found in the latter. The dead space in the system used for constructing the V_D/V_T graph was 100 ml. Had we used a system with a lower dead space, the resulting Pa_{CO_2} might have been higher and the above—mentioned difference in Q would have been lessened.

An indirect method was used to determine whether the corrected V_D/V graph was more suitable for use in the Bohr equation than the original Asmussen-Nielsen graph. This is shown in Table 2, where $\dot{Q}$ values, calculated by using the above-mentioned two graphs, as well as by the end-tidal procedure, are correlated to $\dot{V}_{O_2}$. It is assumed that the method yielding a higher correlation is probably the more accurate one. As seen

Table 2 *Correlation coefficients ( ) bet een $\dot{Q}$ and $\dot{V}_{O_2}$ three d fferent method for determination of Pa_{CO_2}*

Variable (vs. V_{O_2})	r Girls	Boys	all
^{a}end-tidal	676 n=42	785 n=36	714 =78
^{d}Asmussen-Nielsen	060 n=40	.397 n=36	160 n=76
^{c}Corrected graph	570 n=42	771 n=36	.627 n=78

In the Table, the "corrected graph method, although superior to the Asmussen Nielsen procedure, is still somewhat inferior to the end-tidal one.

Until further information is available on V_D of exercising children, it is recommended that the end tidal measurement of Pa_{CO_2} be used as part of the CO_2 rebreathing technique.

LIST OF REFERENCES

1. Ashton, C. H and McHardy G. J R. A rebreathing method for determining mixed enous P_{CO_2} during exercise. *J Appl Physiol 18* 668, 1963.
2. Asmussen, E and Nielsen, M. Physiological dead space and al eolar gas pressures at rest and during exercise. *Acta Physiol Scand 38* 1, 1956
3. Bar-Or, O Shephard, R. J and Allen, C. L. Cardiac output of 10—13 year-old boys and girls during submaximal exercise. *J Appl Physiol 30* 219 1971
4. Ferguson, R J Faulkner, J A., Julius, S. and Conway J Comparison of cardiac output determined by CO_2 rebreathing and dy -dilution methods *J Appl Physiol 25* 450, 1968
5. Jernérus, R Lundin, G and Thomson, D. Cardiac output in healthy subjects determined with CO_2 rebreathing method. *Act Physiol Sc nd 59* 390, 1963
6. Jones, N L., McHardy G J R., Halmark, A. and Campbell, E. J M. Physiological dead space and alveolar-arterial gas pressure differences during exercise. *Clin Sci 31* 19 1966.
7. Klausen, K. Comparison of CO_2 rebreathing and acetylene methods for cardiac output. *J Appl Physiol 20* 763 1965
8. Lundin, G and Thomson, D Determination of the mixed venous CO_2 pressure with rebreathing method. Correction for volume changes of the lung-bag system. *Acta Physiol Scand 64* 440, 1965
9. Magel, J R. and Anderson, K. L. Cardiac output in muscular exercise measured by the CO_2 rebreathing technique. *I* H. Denolin, K. Konig, R. Messin and S. Degré (eds) *Ergometry in Cardiology* Bohringer Mannheim Gmbh, 1968
10. Muiesan, G., Sorbini, C. A., Solinas, E., Grassi, V Casucci, G. and Petz E. Comparison of CO_2 rebreathing and direct Fick methods for determining cardiac output. *J Appl Physiol, 24* 424, 1968.
11. Satoh, I Iwamoto, M. and Oyama, J Determination of cardiac output by rebreathing method with special reference to its reliability and merit in clinical use. *Japan Circ J 32* 1109 1968.
12. Shephard, R. J Allen, C. L Bar-Or O Davies, C. T M., Degré, S., Hedman, R Ishii, K., Kaneko, M., Lacour J. R., di Prampero, P E. and Seliger V The working capacity of Toronto school children. *Canad Med Assoc J 100* 560, 1969.
13. Shephard, R. J and Bar-Or O Al eolar ventilation in near maximum exercise Data on preadolescent children and young adults. *Med Sci Sport 2* 83, 1970.

(O B.-O) Department of Research
Wingate Institute for Physical Education
Wingate Post Office, Israel

Key words Cardiac output in exercise, Pa_{CO_2} in childr en, CO_2 rebreathing

Acta Paediat Scand Suppl 217 1971

CARDIAC OUTPUT DURING EXERCISE IN PUBERTAL BOYS

BENGT O. ERIKSSON

From the Department of Physiology Gymnastik- och idrottshögskolan and Department of Pediatrics at Karolinska institutet St Göran's Children's Hospital, Stockholm Sweden

Two studies were recently published in which the CO_2 rebreathing method was used to determine cardiac output in children during exercise (2, 7) In these studies maximal exercise was not included. It was then felt that it might be of value to perform a study in pubertal boys using the dye-dilution technique and to include maximal exercise as well. A more complete description of the results will be found elsewhere (5)

SUBJECTS AND METHODS

Eight boys, 13—14 years, were studied. The exercise was performed on a Krogh bicycle ergometer Oxygen uptake was determined with the Douglas bag technique. The dye-dilution technique with cardio-green as an indicator substance and the Beckman densitometer as the recording unit was used to determine cardiac output. Details about the method and the equipment used can be found elsewhere (13)

Blood pressure was recorded with the aid a pressure recorder (Elema 490 A) and a Honeywell visicorder. Heart volume was established using a biplane radiographic method, (10, 11) Arterial lactate concentration was determined with an enzymatic method (14) The Astrup technique was used for the determinations of P_{CO_2} base excess and pH in the arterial blood and an electrode for the P_{O_2} measurements. Hemoglobin was determined as oxy hemoglobin with a Beckman spectrophotometer and the calibration curve was obtained by van Slyke analysis.

PROCEDURE

The arterial catheter was inserted approximately 5 cm into the radial or brachial artery of the left arm. The venous catheter was inserted approximately 10 cm into an antecubital vein. The Seldinger technique or a tephlon needle was used. Determinations at rest were performed in the upright position half an hour after the insertion of the catheters and five minutes after changing from supine position. All boys exercised at 300, 600 and 900 kpm/min. For six of the boys a fourth, higher work load was included as the maximal work load.

RESULTS

The cardiac output at rest in a sitting position and its variation with oxygen uptake are illustrated in Fig. 1 There was some individual variation in the material but all the determinations except two values fell under the regression line but within —2 SD when compared with a material of young men (4) Part of the response may be that although the boys were of the same age, their body size and pubertal maturity varied considerably

The mean value for the stroke volume with the subject at rest in a sitting position expressed in

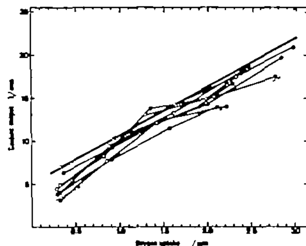


Fig 1 Individual alues on cardiac output in relation to oxygen uptake at rest, during submaximal and maximal exercise in pubertal boys. Unfilled symbols denote rest and submaximal exercise and filled symbols denote maximal exercise. The heavy solid lnte (with ±2 SD) denotes material of young nonathletic men (4)

per cent of the maximum, was 70 (52—90 per cent. But with a relative work load of only 35 per cent of maximal oxygen uptake stroke volume amounted to 95 ±4 (83—99) per cent of its maximal value (87 ml) no further significant increase in stroke volume was observed. However it was of special interest to note that 6 out of the 8 subjects achieved their greatest stroke volume during maximal exercise. In the two subjects who did not reach maximal stroke volume during the heaviest work load, the difference was only 4 ml (<5 %) The mean heart rate when the subjects first attained their maximal stroke volume was ca. 105 beats/min.

There was an almost linear increase in the calculated a v oxygen difference in relation to relative work load with an average value at rest of 7 0 ±1 7 and 14.5 ±1 0 (13.3—15 9) vol % during maximal exercise.

There was a decrease in peripheral vascular resistance with moderate exercise and an increase in the arterial pressure in the four subjects for whom pressure was recorded in the brachial artery Mean values for the mean arterial pressure with subjects at rest was 94 (85—110) mm Hg and it increased with increasing work loads, reaching 129 (125—138) mm Hg during maximal exercise.

The mean value for pH with subjects at rest was 7 39 and changed to 7 35 at 600 kpm/min and 7.27 with maximal exercise. In the corresponding situation P_{CO_2} values were 39 36 and 29 mm Hg and P_{O_2} values 98, 95 and 94 mm Hg respectively Mean hemoglobin concentration was 13 0 g/100 ml with subjects at rest and increased to 13 5 and 14.1 g/100 ml at 600 kpm/min and with maximal exercise respectively Calculated arterial oxygen saturation was then 98, 96 and 94 per cent with subjects at rest 600 kpm/min and maximal exercise, respectively

DISCUSSION

In the present study there was an increase in the cardiac output when subjects went from rest to exercise but absolute values for cardiac output at a given oxygen uptake in these 13—14 years old boys were 1—2 l/min lower than those observed in material comprising adult men (3 4, 9 12, 13) This resulted in a higher a v difference even when the work load was expressed in relative terms, which is in agreement with the mean values obtained with the CO_2-rebreathing technique for the determination of the children s cardiac output (2, 7)

The main explanation for the lower cardiac output found in children is probably the fact that the absolute amount of blood distributed to different tissues or organs is less in persons still growing as compared to adults due to the difference in size. At rest the cardiac index is also very similar in these boys when compared with the values for adults (3 4, 9 12, 13) There tends to be a small difference in cardiac output between the two age groups during submaximal exercise. The reason for this may be that approximately the same amount of blood is distributed to the exercising muscles and the skin at a given submaximal oxygen uptake. Blood flow to organs such as the liver and the kidney are reduced during exercise. Thus, the difference between youths and adults in absolute terms in the total amount of flow to these organs can only be of a minor magnitude.

It has previously been shown that females during exercise compensate their lower hemoglobin con-

centration and oxygen carrying capacity of their blood by maintaining a larger cardiac output (1) The boys in the present study had hemoglobin values in the same range as women, but they displayed greater arterio-venous oxygen difference than those seen in adults. Thus they extract more of the oxygen, resulting in a lower value of the calculated mixed venous oxygen content.

It is worth noting that children have lower blood lactate concentrations during work than full grown persons (6) Moreover arterial pH is not reduced in children to the extent observed in adults either during submaximal or maximal exercise. This must imply a less potent Bohr effect during exercise in children but in spite of this they exhibit a wider oxygen difference. How this is brought about is not known, but may lend support to the hypothesis that relatively more of the cardiac output during exercise is distributed to the active muscles in the children than in adults.

SUMMARY

Eight boys, 13—14 years old, were studied with determinations of cardiac output (dye-dilution technique) arterial blood pressure and blood gases during submaximal and maximal exercise on a bicycle ergometer. At maximal exercise oxygen uptake was 2.5 l/min, cardiac output 17.4 l/min, heart rate 200 beats/min, stroke volume 87 ml and arteriovenous oxygen difference 14.5 vol %. The stroke volume at 35 per cent of maximal oxygen uptake (heart rate 105 beats/min) did not differ from the maximal stroke volume. Cardiac output at a given oxygen uptake during exercise was 1—2 l/min below the average values in adult men. The gas exchange studies showed results similar to those in adult men.

Key Words

Stroke volume, arterio-venous oxygen difference, arterial blood pressure, arterial blood gases, heart volume, maximal oxygen uptake, testicular volume index.

REFERENCES

1. Astrand, P-O Cuddy E., Saltin, B and Stenberg, J Cardiac output during submaximal and maximal work. *J appl Physiol,19* 268, 1964.
2. Bar-Or O., Shephard, R. and Allen, C. Cardiac Output of 10 to 13 Year-old Boys and Girls during Submaximal Exercise. *J appl Physiol*, 1971 In press.
3. Bevegård, S. Studies on the regulation of the circulation in man. *Acta Physiol Scand 57* Suppl. 200, 1962
4. Ekblom, B Astrand, P-O Saltin, B., Stenberg, J and Wallström, B. M Effect of training on circulatory response to exercise. *J appl Physiol 24* 518, 1968
5. Eriksson, B O Grimby G and Saltin, B Cardiac output and arterial blood gases during exercise in pubertal boys. *J appl Physiol* 1971 In press.
6. Eriksson, B. O Karlsson, J. and Saltin, B. Muscle metabolites during exercise in 13 year old boys. *J Appl Physiol* To be published.
7. Godfrey S. M., and Davies, C. T M.: Estimate of arterial P_{CO_2} and their effect on the calculated values of cardiac output and dead space on exercise. *Clin Sci* 39. 529 1970.
8. Granath, A Jonsson, B. and Strandell, T Circulation in healthy old men, studied by right heart catheterization at rest and during exercise in supine and sitting position. *Acta Med Scand 176*. 425 1964.
9. Grimby G. Exercise in man during pyrogen induced fever. *Scand J Clin Lab Invest 14*. Suppl 67 1962.
10. Kjellberg, S. R., Rudhe, U and Sjostrand, T., The relation of the cardiac volume to the weight and surface area of the body the blood volume and the physical capacity for work. *Acta Radiol, 31* 113 1949
11. Kjellberg, S. R., Lind, J Lönnroth, H. and Rudhe, U Variations in heart volume in normal children of school age *Acta Radiol 41* 441 1954.
12. Rowell, L. B *Factors affecting the prediction of maximal oxygen intake from measurements made during submaximal work with observations related to factors which may limit maximal oxygen intake* (Thesis) Minneapolis. University of Minnesota, 1962.
13. Saltin, B Blomqvist, G Mitchell, J H. Johnson, R L Wildenthal, K. and Chapman, C. Response to exercise after bedrest and training. *Circulation, 38*. Suppl VII, 1968
14. Scholz, R Schoetz, H., Bücher, T and Lampen, J-O. Über die Wirkung von Nystatin auf Bäckerhef *Biochem Z, 331* 71 1959

(B E.) St Göran Children Hospital
Box 125000, S-112 81 Stockholm, Sweden

ERGOMETRY AND PHYSICAL TRAINING IN PEDIATRICS WITH SPECIAL REFERENCE TO PULMONARY FUNCTION

JAN BJURE

From Department of Clinical Physiology Childrens H spital, Göteborg, Sweden

There is a huge l terature concerning ergometry and training in general and it is mainly concerned with the effect of exercise on peripheral and central circulation. The effect of training is usually judged from changes in for example heart rate, cardiac output, stroke volume, oxygen uptake and lactic acid. However the respiratory function during exercise up to maximum and after training is very little analyzed. The possible role of the lungs in limiting oxygen transport at maximal levels of exercise is often neglected both in healthy subjects and in patients.

Since it is quite impossible to cover the whole field I will restrict myself to the lungs in ergometry and physical training and to consider what will happen during aging after childhood and adolescence.

Before the first breath, the lungs are filled with fluid, and large negative pressure is necessary to get air into the lungs. With each breath the lungs will be more filled with air and the functional residual capacity is rapidly at first, later more slowly built up to reach a value of about 0.1 l during the first three hours. The oxygen uptake increases during the first minutes and reaches a value of around 50 ml after about 10 minutes. A little later the oxygen uptake decreases and reaches a level which is half the value about 10 minutes after birth. The breathing frequency slows down, arterial oxygen saturation and carbon dioxide ten sion reach values normal for that age These findings during the first hour compares well with what happens a little later when maximal oxygen uptake was measured in the child stimulated in an appropriate way (12) The basal oxygen uptake in the newborn is about 20 ml pr minute and the maximal oxygen uptake is about 40 ml, a figure which agrees well with the oxygen consumption the child had shortly after birth. As the child grows up the gap between basal and maximal oxy gen uptake widens. The normal child is able to double his oxygen consumption. The grown up child is able to increase his oxygen uptake almost 15—20 times.

The dimensional relationship of the lungs at different age gives some interesting aspects. The newborn child has about 24 million alveoli with a surface area of about 2.8 m^2 (8) During the following months the number of alveoli increases markedly and has at the age of 4 years increased about 10 times compared with the number at birth with a concommitant increase in area of about 8 times. After the age of 4 t is especially the area which increases. The number of alveoli at this age are almost the same as for the adult. The number of alveoli increases 12 times and the area of alveoli about 27 times from birth to adult age.

The development of functional dimensions through childhood and adolescence can be il lustrated with the growth of lung volumes. The increase in vital capacity shows a good correlation with the cube of the height with a general trend

of somewhat higher values in boys. At a height of about 150 cm the increase in vital capacity in boys ceases temporarily and is lagging after the increase in height during the prepubertal growth. The vital capacity increases with age and height and reaches maximal values around 20—25 years of age after which age the values steadily decrease (3) The same curve can supposedly illustrate the change of maximal oxygen uptake or maximal pulmonary transfer factor with age.

It is interesting to compare the pulmonary transfer factor earlier called diffusing capacity for the newborn at rest and that for the adult man at maximal work. To get the same dimensions of the figures the transfer factor is given per liter functional residual capacity (FRC) According to G Koch (13) the transfer factor for the newborn infant is about 2.1 ml/(min mm Hg) which with an FRC of 0.1 l gives 21 ml/(min mm Hg) as the transfer factor per l FRC. For a 25 years old man a value of about 23 ml/min mm Hg) for the transfer factor per l FRC at maximal work can be regarded as normal l FRC = 2.8 l (10) transfer factor taken to be about 65 (cf 15) The corresponding figure for a 52 years old man was found to be 14 (4) This indicates that the normal newborn child at rest is close to its maximal transfer factor and the child at rest has the pulmonary capillary bed almost maximally expended. In accordance with this view is the observation (12) of only a small difference in oxygen uptake between rest and maximal crying, indicating that the child has a small reserve capacity of the pulmonary capillary bed. According to Englert (9) the single breath transfer factor at rest increases up to the age of 25 years, reaching a value of about 25 after which age it slightly decreases. As discussed above the maximal transfer factor reaches a value of about 65 at the age of 25 years. This may be compared with the value of 47 at the mean age of 52 (4) Thus the gap between the transfer factor at rest and during maximal exercise increases up to the age of 25 years and then decreases. Thus we start and end our life with small pulmonary reserves.

The question arises if with training at any special age it is possible to increase the size of the lungs. It is then natural that the effect of training in both children and adults is dependent on what age the training starts and also on the physical fitness at the beginning of the training period. The crying of the newborn baby may be a good training. The child at the age of 1—3 years has with jumping and running around many periods of hard training during the day The development of the child is in itself a period of hard training

The next period of interest is during the pre pubertal growth spurt at what time values are lagging after Is it with training possible to influence the size of functional dimensions during this period? This will be discussed later during the symposium.

There is a matter of dispute if patients with lung disease should be trained. Patients with lung disease primary or secundary to thoracic deformaties and congenital heart disease with or without right to left shunts are usually without bronchial obstruction. With increasing severity of the disease the pulmonary capillary bed will be more restricted, the reserve capacity will be more reduced and the pulmonary artery pressure will be pathologically elevated, first during exercise, later also at rest. The question arises if training will make their situation even worse by increasing the pulmonary artery pressure and by lowering arterial oxygen saturation.

It is known that the ventilation is unevenly distributed in the lungs in the sitting position with the basal parts having about 1 1/2 times greater ventilation than the apical ones. (14) In the supine position dorsal parts are better ventilated than ventral parts. As to the perfusion basal parts are 3 to 5 times better perfused per lung volume than apical parts (16) During increasing exercise the perfusion is more evenly distributed and in normal healthy subjects the base-apex quotient approaches 1 that is the same perfusion per volume in apical and basal parts (2)

This difference in distribution of ventilation and perfusion at rest results in the well known ventilation-perfusion inequalities in the lungs. At the bottom of the lungs there is more blood flow than ventilation, i.e. alveolar hypoventilation, and at the

apex there is more ventilation than blood flow i.e. alveolar hyperventilation. From available data in the literature it may be assumed that ventilation has almost the same distribution during exercise as at rest in normal subjects. With increasing exercise perfusion becomes more even resulting in a more even distribution of ventilation to perfusion throughout the lung. Although during maximal exercise in healthy subjects arterial oxygen saturation is not decreased the finding of the marked increase in alveolo-arterial oxygen tension difference clearly indicates a burden on the respiratory system (4)

With increasing age more blood are distributed to the apical parts of the lungs in normal subjects. In patients with lung disease finally leading to pulmonary artery hypertension this will happen earlier The same type of ventilation perfusion inequality as during maximal exercise in normal subjects will appear during moderate exercise or even at rest. In patients with mitral valvular disease this pathological distribution of perfusion is positively correlated to the pressures in left atrium and pulmonary artery (11) The basal parts of the lungs are thus less perfused because of pulmonary vascular constriction in these areas. We have studied the distribution of blood flow in patients with mitral stenosis sitting at rest, during exercise and after exercise (7) It was found that those patients with a perfusion qoutient below 1 between base and apex in fact increased their basal perfusion during or even more after exercise. This must indicate that these patients are able to dilate their basal constricted vessels. From these results it seems advisable to train patients with pulmonary artery hypertension as early as possible in the course of the disease with the aim to prevent the occurence of anatomical vascular changes. Since these patients have later in the course of the disease a reduced reserve capacity of their lungs the effect of training on their physical performance will be small. This matter can be illustrated by the effect of training in young patients with idiopathic scoliosis Most of the patients increased their maximal oxygen uptake in the ordinary way but there were som patients with no or only moderate increase of oxygen uptake These patients were found among those with the largest curvatures and had ventilatory limitation of their physical performance (6)

During the last years we have studied the distribution of ventilation and perfusion in a large group of patients with idiopathic scoliosis of different ages (6, 5 1)

The results are such that we can learn a lot of how to treat patients with this disease, which sooner or later leads to pulmonary artery hypertension. With increasing curvature there is a reduction in lung volumes. Vital capacity is reduced approximately to the same extent as total lung capacity Using the ^{133}Xenon method we found that with increasing curvature the basal parts are less ventilated, which is also reflected in the lower perfusion of the most basal part in patients with the largest curvatures.

It seems reasonable to believe that these patients have primarily a basal hypoventilation which leads to basal vasoconstriction and distribution of blood from basal to apical parts. Patients with the largest curvatures have airway closure in basal areas during normal quite breathing It is then advisable to instruct these patients to regularly make deep breathing maneuvres in order to open up and ventilate more or less collapsed airways, with a dilating effect also on the vessels Ordinary training program should also be included in the therapeutic arsenal. The low working capacity as we noted in our study from the start is probably common in scoliotic patients, which can be accounted for by different somatic reasons. It is common clinical observation that these patients suffer mentally from their deformity and they take seldom part in physical activities.

Knowledgement of the respiratory and circulatory function of patients with lung disease is necessary before we advise them to training Since the number of patients for training is steadily increasing we had to decide which methods should be used in order to maintain adequate standard with unnecessary straining the patients and available laboratory resources.

As a screening of respiratory and circulatory function I would suggest.

1. Studies including spirometry and tests of working power combined with

2. Analysis of arterial or capillary blood for oxygen and carbon dioxide tensions.

During the training period we should follow the patients regularly with screening tests to be informed about the effect of training on lung function in children with lung disease.

When introducing training in the treatment of many of our patients there are some points I want to make.

1. We must increase our knowledge about the effect of training in children with different disorders and in different ages.

2. If we have found that training is favourable for the child we must define optimal training programs for these groups.

REFERENCES

1. Bake, B., Bjure, J., Kasalicky, J. and Nachemson, A.: Regional distribution of ventilation and perfusion in patients with untreated idiopathic scoliosis (To be published)
2. Bake, B., Bjure, J. and Widimsky, J.: The effect of sitting and graded exercise on the distribution of pulmonary blood flow in healthy subjects studied with the 133Xenon technique. *Scand J Clin Lab Invest* 22. 99. 1968.
3. Berglund, E., Birath, G., Bjure, J., Grimby, G., Kjellmer, I., Sandqvist, L. and Söderholm, B.: Spirometric studies in normal subjects. I. Forced expirograms in subjects between 7 and 70 years of age. *Acta Med Scand*, 173. 185. 1963.
4. Bjure, J., Grimby, G. and Nilsson, N. J.: Pulmonary gas exchange during submaximal and maximal exercise in healthy middle-aged men. In Exercise diffusing capacity of the lungs. Huber 1971.
5. Bjure, J., Grimby, G., Kasalicky, J., Lindh, M. and Nachemson, A.: Respiratory impairment and airway closure in patients with untreated idiopathic scoliosis. *Thorax*, 25. 451, 1970.
6. Bjure, J., Grimby, G. and Nachemson, A.: The effect of physical training in girls with idiopathic scoliosis. *Acta Orthop Scand*, 40. 325. 1969.
7. Bjure, J., Lunder, B. and Widimsky, J.: The effect of exercise on the distribution of pulmonary blood flow in patients with mitral stenosis. *Brit Heart J* 33. 000, 1971.
8. Dunnil, M. S.: Postnatal growth of the lung. *Thorax* 17. 239. 1962.
9. Englert, M.: L'influence de l'âge sur la capacité de diffusion pulmonaire chez l'homme normal. *Med Thorac* 21. 1, 1964.
10. Grimby, G. and Söderholm, B.: Spirometric studies in normal subjects. III. Static lung volumes and maximum voluntary ventilation in adults with a note on physical fitness. *Acta Med Scand* 173. 199. 1963.
11. Jebavy, P., Runczik, L., Oppelt, A., Stanek, V., Tilsch, J. and Widimsky, J.: Regional pulmonary function in patients with mitral stenosis in relation to haemodynamic data. *Brit Heart J* 32. 330, 1970.
12. Karlberg, P.: Development anatomy and physiology of the lungs. *The biological basis of pediatric practice.* McGraw-Hill, New York 1968, vol. 1. p. 283.
13. Koch, G.: Lung function and acid-base balance in the newborn infant. *Acta Paediat Scand* Suppl. 81. 1968.
14. Milic-Emili, J., Henderson, J. A. M., Dolovich, M. B., Trop, D. and Kaneko, K.: Regional distribution of inspired gas in the lung. *J Appl. Physiol*, 21. 749. 1966.
15. Newman, F., Smalley, B. F. and Thomson, M. L.: Effect of exercise body lung size on CO diffusion in athletes and nonathletes. *J Appl Physiol* 17. 649. 1962.
16. West, J. B.: Topographical distribution of blood flow in the lung. *In American Physiol Soc Handbook of Physiology*. Section 3, Respiration vol II. Washington, 1965. p. 1437.

(J.B.) Dept. Clin. Physiology
Barnsjukhuset, S 413 46 Goteborg, Sweden

Key word: Ergometry physical training pulmonary function.

Acta Paediat Scand Suppl 217 1971

PHYSICAL TRAINING IN NORMAL BOYS IN ADOLESCENCE

By BJÖRN EKBLOM

From the Department of Physiology Gymnastik- och Idrott högskolan Stockholm Sweden

The present study (4) was initiated by the fact, that the maximal oxygen uptake in a grown-up healthy population can range from 30—35 ml in untrained persons up to over 85 ml in athletes from endurance events (3) But in training studies the increase in maximal oxygen uptake has only been about 15—20 up to 30 % (5 6, 7 and others) In almost all of these training studies the training program has lasted from a few weeks up to half a year or so, but even if the training program is extended over several years (Fig 1) the maximal oxygen uptake seems to reach an individual maximal plateau, which is far below that of the endurance event athletes. So it seems that if the physical training is started in the grown-up man, there might be an upper limit, over which one cannot go, even if the physical training is very hard and extended over many years. The question is then When in life is this limit set? Is it only determined by genetic factors, or can this limit be influenced by i.e. physical training before and during the puberty?

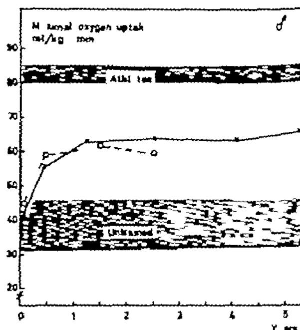


Fig 1 The increase in maximal oxygen uptake as an effect of long-term physical training in 2 boys (19 and 22 years of age at the start) compared with maximal oxygen uptake in endurance event athletes (3) and grown-up untrained individuals

MATERIAL

In order to penetrate this problem we had 14 boys from the same class in an elementary school in Stockholm, all 11 years of age at the start, who volunteered for this physical training study 7 boys were placed in the training group and the other 7 boys were used as controls During the first 6 months of this study the training group had special supervised physical training 3 times a week. Beside that both the training and the reference group had physical training in school 2 times 45 min a week. After the first 6 months 5 boys from the original training group and 2 boys from the reference

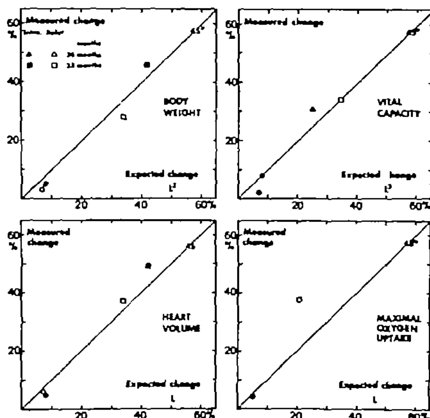


Fig 2. Group mean values of measured increase of body weight, vital capacity heart volume and maximal oxygen uptake and corresponding expected change, as predicted from the increase in body size. L and L refer to the expected increase for the different dimensions from the relation body height after to body height before the observation period, raised to 2.0 and 3.0, respectively

group continued to train in different ball game clubs, in average they had training and matches 3 times a week. Before the training and after 6 months and 32 months all boys underwent different tests in the laboratory

RESULTS AND DISCUSSION

The present study started when the subjects were about 11 years old and extended over 32 months. With an observation period such as this there are age-dependent physical and physiological growth which must be taken into account, and which add to the difficulty of evaluating the effects of physical training as distinct from the age-dependent increase of the different physiological parameters. Owing to individual variations and for other reasons it is not possible to determine the effect of the physical training by simply comparisons of the differences between the increases in the parameters studied in the two groups.

It is a well-known fact, however that the relative length of different body lengths in 10 year old and in a 15 year old boy are on the whole proportional. Therefore if theoretically we consider these two categories of boys to be geometrically similar and qualitatively identical, we may firstly assume that all corresponding linear dimensions will be proportional and secondly that in comparing corresponding areas and volumes in these two individuals the same relation will be shown as for corresponding body lengths (e g body height) raised to 2.0 and 3 0 respectively (for further discussion, see 1) As regards volume, it can be demonstrated by transposing this approach to Astrand's study on Swedish school-children (2) that the theory has validity also for vital capacity and body weight. If the 14—15 years group in Astrand's study is compared with the 10—11 year group, it will be found that the relation of body weight and vital capacity between the older group and the younger group is the same as for the two

groups body heights raised to 2.8 and 3.0, respectively (theoretical value for both is 3.0) Now if we compare a 170 cm tall boy with another boy of 187 cm—the difference in heigth is 10 %. Now according to Asmussen and Heeboll Nielsen (1) a volume measurement of the taller boy should related to the heart volume of the smaller boy as the height relation of the two boys in the third power. That is $(187/170)^3 = 1.33$ The taller boy should have a 33 % larger heart volume, vital capacity blood volume, body weight etc.

This discussion can be used in the present study to separate an eventual training effect from the normal growth in different measurements. Using the individuals height at different times of this study we can estimate the expected normal increase in different measurements and than compare this expected value with the measured value.

Fig 2 shows this expected value compared with the measured one. Only mean values for the different observation period and the different groups have been used.

We shall first look at the reference group since this group have had very little training and we therefore can use this group to see whether this way of estimating the expected values is adequate or not. As seen in body weight, vital capacity and heart volume—which all should be related to the length scale (that is height relation) in the third power there is a good agreement between expected and measured values. However, in the training group the measured values for heart volume and vital capacity for the longer observation periods, 26 and 3 months, exceed that of the expected value. This might therefore be an effect of the physical training.

SUMMARY

Physical training before and during puberty seem to increase different dimensions as heart volume and vital capacity and functional capacities as maximal oxygen uptake more than what could be expected from the normal growth.

REFERENCES

1 Asmussen, E., and Heeboll-Nielsen, K. A dimentional analysis of physical performance and growth in boys. *J Appl Physiol, 7* 593, 1955
2 Astrand, P.-O *Experimental studies of physical working capacity relation to sex and age* Munksgaard, Copenhagen, 1952.
3 Astrand, P-O and Saltin, B., Maximal oxygen uptake in athletes. *J Appl Physiol* 23. 353, 1967
4. Ekblom, B Effect of physical training in adolescent boys. *J Appl Physiol* 27 350, 1969
5 Ekblom, B Astrand, P-O Saltin, B., Stenberg, J and Wallström, B. Effect of training on circulatory response to exercise. *J Appl Physiol, 24.* 518, 1968.
6. Robinson, S., and Harmon, P M. The effects of training and of gelatin factors which limit muscular work. *Am J Physiol 133.* 161, 1941
7 Saltin, B Blomqvist, J H., Mitchell, R., Johnson Jr R Wildenthal, K., and Chapman, C. B. Response to submaximal and maximal exercise after bed rest and training. *Circulation, 38* suppl 7 1968

(B E.) Fysiologiska Institutionen, Gymnastik och Idrottshögskolan, Lidingövägen 1 114 33 Stockholm, Sweden.

Key words Physical training, growth, maximal oxygen uptake, heart volume, vital capacity

Acta Paediat Scand Suppl 217 1971

THE INFLUENCE OF AGE AND SPORTS TRAINING IN SWIMMING ON PHYSICAL FITNESS

V SOBOLOVA, V SELIGER, D GRUSSOVA, J MACHOVCOVA and V ZELENKA

From the Department of Physiology Faculty of Physical Education and Sports Charles' University Prag Czechoslovakia

The physical fitness of the athlete's organism is be influenced by a number of factors involving both the growth and the character and intensity of exercise such as sports training.

Several groups of swimmers enabled us to evaluate the influence of various factors on physical fitness. Swimming is a sport which produces a significant intensity of adaptation impulses (3). A number of papers have been devoted to the investigation of the influence of swimming on the organism's function (9 16). It appears that swimming accelerates functional development in proportion to the intensity and extent of training, this cause of the fact that swimming training provides almost maximal activation of aerobic and anaerobic processes (3).

MATERIAL AND METHODS

We examined a total of 43 boys and men and divided them into four age groups according to age and the length of swimming training; the groups were 13, 14, 15 and 19 years. Boys 13 to 15 years of age took part in regular sports training at experimental schools. The training took 10 hours per week on average and was conducted by specialized trainers.

Fundamental somatic indices, as listed in Table 1, were measured in all the groups. Heart rate, oxygen uptake, pulmonary ventilation and other indices were examined in rest with the subject sitting still on the bicycle ergometer and with subjects pedalling with graduated loads until subjects' exhaustion was reached. The pedalling rate was 60 rpm. We used three submaximal loads, each lasting 6 minutes. The first load amounting to 1.0—1.5 W/kg body weight and each subsequent load 0.5 W/kg body weight more. The maximal load was usually 50—100 W more than the

Table 1 *Physical characteristics of experimental subjects*

	13 years (n=11)		14 years (n=12)		15 years (n=10)		19 years (n=10)	
	x	SD	x	SD	x	SD	x	SD
Height (cm)	156	8.0	166.3	4.2	172.6	4.7	183.0	6.8
Weight (kg)	42.7	5.4	53.4	6.1	60.5	5.5	77.1	7.7
LBM (kg)	36.8	4.4	45.9	5.6	52.0	4.5	67.4	5.6
Fat (%)	13.6	2.0	14.2	2.2	13.7	1.1	12.4	2.5
BSA (m^2)	1.34	0.12	1.54	0.09	1.67	0.09	1.98	0.12
VC (ml)	3259	595	4226	684	4785	499	5801	826
W 170 (W)	148.3	41.0	187.6	46.2	227.0	27.8	232.6	40.8
W 170/kg (W)	3.5	0.96	3.5	0.86	3.8	0.46	3.0	0.53

groups body heights raised to 2.8 and 3.0, respectively (theoretical value for both is 3.0). Now if we compare a 170 cm tall boy with another boy of 187 cm—the difference in heigth is 10 %. Now according to Asmussen and Heeboll-Nielsen (1) a volume measurement of the taller boy should related to the heart volume of the smaller boy as the height relation of the two boys in the third power. That is $(187/170)^3 = 1.33$. The taller boy should have a 33 % larger heart volume, vital capacity, blood volume, body weight etc.

This discussion can be used in the present study to separate an eventual training effect from the normal growth in different measurements. Using the individuals height at different times of this study we can estimate the expected normal increase in different measurements and than compare this expected value with the measured value.

Fig . shows this expected value compared with the measured one. Only mean values for the different observation period and the different groups have been used.

We shall first look at the reference group since this group have had very little training and we therefore can use this group to see whether this way of estimating the expected values is adequate or not. As seen in body weight, vital capacity and heart volume—which all should be related to the length scale (that is height relation) in the third power there is a good agreement between expected and measured values. However in the training group the measured values for heart volume and vital capacity for the longer observation periods, 26 and 32 months, exceed that of the expected value. This might therefore be an effect of the physical training.

SUMMARY

Physical training before and during puberty seem to increase different dimensions as heart volume and vital capacity and functional capacities as maximal oxygen uptake more than what could be expected from the normal growth.

REFERENCES

1. Asmussen, E., and Heeboll-Nielsen, K. A dimentional analysis of physical performance and growth in boys. *J Appl Physiol*, 7 593, 1955
2. Astrand, P.-O. *Experimental studies of physical working capacity in relation to sex and age* Munksgaard, Copenhagen, 1952.
3. Astrand, P.-O. and Saltin, B. Maximal oxygen uptake in athletes. *J Appl Physiol* 23. 353, 1967
4. Eklom, B., Effect of physical training in adolescent boys *J Appl Physiol* 27 350, 1969
5. Eklom, B. Astrand, P.-O. Saltin, B., Stenberg, J., and Wallström, B. Effect of training on circulatory response to exercise. *J Appl Physiol* 24. 518, 1968
6. Robinson, S., and Harmon, P. M. The effects of training and of gelatin factors which limit muscular work. *Am J Physiol* 133. 161, 1941
7. Saltin, B., Blomqvist, J. H., Mitchell, R. Johnson Jr., R., Wildenthal, K., and Chapman, C. B. Response to submaximal and maximal exercise after bed rest and training. *Circulation* 38, suppl 7 1968.

(B.E.) Fysiologiska Institutionen, Gymnastik- och Idrottshögskolan, Lidingövägen 1, 114 33 Stockholm, Sweden.

Key words: Physical training, growth, maximal oxygen uptake, heart volume, vital capacity

Table 3 F ctional alues at st and nder load th bicycl ergom t —14 years old boys

	rest		1.load		2.load		3.load		max.load	
	x	S D	x	S D	x	S D	x	S D	x	S D
W load	—	—	33.6	6.4	60.1	9.1	107.6	12.5	273.4	43.6
HR, beats/min	77.5	13.2	104.8	12.8	122.0	14.5	132.1	14.9	191.0	9.1
BP mm Hg	121.1	8.9	136.7	10.1	142.5	12.7	150.0	13.5	165.5	19.8
V L	0.73	0.29	1.21	0.18	1.27	0.24	1.33	0.16	1.99	0.48
V	12.4	4.6	23.4	2.2	27.8	3.7	33.3	5.5	80.4	18.4
R Q	0.93	0.20	0.81	0.04	0.84	0.03	0.87	0.05	1.02	0.07
V 2	0.31	0.05	0.94	0.10	1.13	0.12	1.28	0.15	2.76	0.59

and 50 ml/min kg These values generally agree with those reported from Sweden (2) and Czechoslovakia (6, 8) However, they are lower than the values presented in studies of adolescent boys with higher levels of performance 1 9)

The values for oxygen pulse increased with increasing load intensity The slope of the increase and, consequently the level they attained proved to be lower in the 13-year olds than in the other groups.

Heart at increased linearly with increasing load intensity and its slope decreased with increasing age. Small differences between the curves for the 15- and 19-year olds, were most probably due to the high degree of cardiovascular adaptation in the 15-year old well trained swimmers. Maximal values (188, 190 185 and 188 respectively) proved to be practically the same in all age groups concerned. On the whole, they agreed well with data for adult swimmers (9 10) but were lower than the age standards set by Astrand (2) We assume that this is connected with a faster functional development as proposed by Astrand *t al* (3)

Work capacity at the heart rate of 170 beats/min (W_{170}) did not differ from the values obtained according to the modified Rutenfranz equation (11) A comparison of W_{170}, as attained in our four age groups (148, 188, 227 and 233 W respectively) shows that there is no practical difference between the 15 and 19-year old swimmers. I comparison to the Canadian population (6) our groups displayed a substantially higher W_{170} and belong to the category of highly adapted individuals, as far as the fitness of the cardiovascular system and the general endurance is concerned.

The values for W_{170} related to kg body weight (3 5 3 5 3 7 and 3 0 W_{170}/kg respectively) show in comparison to the values and standards assessed for our athletes (15) that the 13- to 15-year olds displayed very good f'tness and the 19-year olds better than average fitness.

SUMMARY

43 male subjects were divided into four age groups (13 14, 15 and 19 years) and the length of sports training in swimming.

Most swimmers have a tall figure and are of medium weight. The fat percentage ranges from 14.2 to 12.4 and is dependent on both the age and the length of sports training. Vital capacity increases with age from 98 to 128 % basal metabolic rate. Maximum pulmonary ventilation increased with age from 65 to 126 liters per minute. Respiratory rate in the younger subjects, tidal volume in the older subjects played the major roles n the in creased in ventilation. In the 13-year olds maximal oxygen uptake was 45 ml/min kg and in the other groups 50 to 51 ml/min kg. Maximal heart rate ranged from 185 to 190 beats per minute. Work capacity at the heart rate of 170 beats/min increased with age from 148 to 233 W

REFERENCES

1 Adams, F H Bengtsson, E Berven, H and Wegelius, C. The physical orking capacity of normal school-children II Swedish city and country *Pediatrics 22* 243, 1961

2 Adams, F H Linde, L M and Miyaki, H. The physical working capacity of normal school-children I California, *Pediatric* 28 55 1961

3 Allard, G and Goulet, C Physical orking capa-

Table 4. Functional indices at rest and under load with bicycle ergometer—15 years old boys

	rest		1.load		2.load		3.load		max.load	
	$\bar{x}$	S.D	$\bar{x}$	S.D	$\bar{x}$	S.D	$\bar{x}$	S.D	$\bar{x}$	S.D
W load	—	—	60.5	5.6	90.6	8.5	120.9	11.0	286.9	33.6
HR, beats/min	75.1	11.1	97.6	9.1	109.4	10.7	124.6	11.4	185.0	17.2
BP mm Hg	123.0	8.9	136.0	11.0	141.5	7.1	155.0	11.1	172.2	21.1
V_T L	0.84	0.24	1.30	0.38	1.52	0.40	1.73	0.38	2.35	0.47
V_E	13.0	5.3	26.7	5.3	31.1	4.5	36.0	6.3	90.1	26.3
R Q	0.96	0.144	0.88	0.08	0.89	0.05	0.86	0.03	1.00	0.09
V_{O2}	0.35	0.07	0.92	0.14	1.17	0.17	1.45	0.21	3.08	0.39

Table 5. Functional indices at rest and under load on the bicycle ergometer—19 years old boys

	rest		1 load		2.load		3 load		max load	
	$\bar{x}$	S.D	$\bar{x}$	S.D	$\bar{x}$	S.D	$\bar{x}$	S.D	$\bar{x}$	S.D
W load	—	—	114.4	18.6	156.3	15.4	195.3	19.2	355.1	38.7
HR, beats/min	78.4	8.5	110.2	9.7	132.4	7.8	152.9	10.1	188.0	8.4
BP mm Hg	118.0	8.2	133.5	13.4	161.0	15.8	181.0	25.5	201.0	30.0
V L	0.93	0.35	1.73	0.40	2.15	0.56	2.66	0.63	3.56	0.55
V_E	12.35	1.9	38.49	5.3	47.5	4.2	64.2	6.6	126.0	23.9
R Q	0.79	0.08	0.83	0.05	0.89	0.07	0.90	0.02	1.13	0.07
V_{O2}	0.37	0.05	1.67	0.18	2.02	0.17	2.63	0.18	3.86	0.40

city in French Canadian population. An epidemiologic study. *För. ar. med. crit.* 3 209 1967

4. Allen, C., Bar-Or O. Davies, C. T. M., Degré, S., Hedman, R., Ishii, K., Kaneko, M., Lacour R., Di Prampero, P. Seliger, V. and Shephard, R. J. Community studies of working capacity in schoolchildren. *Mal. Cardiovasc.* 20 437 1969

5. Andersen, K. L. Work capacity of selected populations. *I* Barker, P. T. and Weiner, J. S. (eds) *The biology of human adaptability* Oxford, 1966, p. 67

6. Åstrand, P. O. *Experimental studies of physical working capacity in relation to sex and age* Copenhagen, 1952

7. Bengtsson, E. The working capacity in normal children, evaluated by submaximal exercise on the bicycle ergometer and compared with adults. *Acta Med Scand* 154 91 1956

8. Howell, M. Z. and MacNab, R. B. *The physical work capacity of Canadian children aged 7 to 17* Canad Ass Health Phy. Educ Recreation 1968.

9. Knuttgen, H. G. Aerobic capacity of adolescents *J appl Physiol* 22 655 1967

10. MacNab, B. J. Conger P. R. and Taylor P. S. Differences in maximal and submaximal work capacity in men and women *J appl Physiol* 27 644, 1969

11. Mácek, M. and Vávra, J. The comparison of the W170 values during growth. *J Sport Med Phys Fitness*, in press 1971.

12. Mocellin, R. and Rutenfranz, J. Methodische Untersuchungen zur Bestimmung der körperlichen Leistungsfähigkeit (W170) im Kindesalter *Z Kinderheilk*, 108 61, 1970

13. Morse, M., Schultz, F and Cassels, D. Relation of age to physiological responses of the older boy (10—17 years) to exercise *J appl Physiol* 1 683, 1949

14. Robinson, S. Experimental studies of physical fitness in relation to age. *Arb Physiol* 10 251, 1938.

15. Rous, J. Matejkova, J. Placheta, Z. Bláhová, D. Kocnar K., Dražil, V. and Vitek, D. The effect of sports training on the working capacity in various sports. *Teor Praxe tel Vych* 16, suppl. 1 26, 1968.

16. Rutenfranz, J. *Entwicklung und Beurteilung der körperlichen Leistungsfähigkeit bei Kindern und Jugendlichen* Biblioth Pediat, Fasc. 82, Karger, Basel, 1964

17. Rutenfranz, J. and Mocellin, R. Untersuchungen über die körperliche Leistungsfähigkeit gesunder und kranker Heranwachsender I. Bezugsgrößen und Normwerte *Z Kinderheilk* 103 109 1968

18. Seliger, V The influence of sports training on the efficiency of juniors. *Int Z A g w Phy ol 26* 309 1968
19 Seliger V and al Physical fitness of Czechoslovak children at 12 and 15 years of ge. International Biological Programme—results of investigations 1968—1969 Acta universitatis Carolinae—gymnica 2, 1970
20. Soulek, V Rating of the alues PWC 170 (Czech) *Teor Prax Tel V y b 17* 622, 1969
21 Szigy A Rosca, E Artunescu, L and Minescu, T Zur Aussagekraft einiger bei submaximaler Belastung angefuhrter ergometrischer Tests fur die Beurteilung der Leistungsfähigkeit bei Spitzensport lern. *Med Sport (Berlin)* 10 17 1970.
22. Weiner J S. and Lourie, J A. IBP Handbook No 9—Human biology *A g ide to field methods.* Oxford, 1969

(V.S) Department of Physiology
Faculty of Physical Education and Sports
Ujezd 450, Praha
Czechoslovakia

K y *ords* Physical fitness, submaximal and maximal work, oxygen uptake, boy 12—15 years.

A PHYSIOLOGICAL ANALYSIS OF FORMER GIRL SWIMMERS

BENGT O ERIKSSON INGA ENGSTRÖM, PETTER KARLBERG BENGT SALTIN and CLAES THORÉN

From the Departments of Paediatrics of Karolinska institutet at St Görans Hospital and Karolinska Hospital Stockholm Department of Paediatrics University of Göteborg, and Department of Physiology Gymnastik- och Idrottshögskolan Stockholm Sweden

The mean age of the best female swimmers in Sweden was around 20 years in 1950 but decreased during the following 10 years to about 15 years of age Competition results improved during the same period of time. Thirty of the best girl swimmers were studied in 1961 with special reference to their respiratory and circulatory adaptation (3) These girls had started their training when they were as young as ten to thirteen years old. Their training was very hard and they spent up to 26 hours a week training.

In relation to their ages and body sizes the girl swimmers had increased lung, blood, and heart volumes. These deviations were significantly correlated to each other and also to the girls maximal oxygen uptakes. Functional development was related to the duration and intensity of training and also to each specific studied functional deviation when the others were held constant. Moreover good correlation was observed between maximal oxygen uptake and results achieved by these swimmers in competition.

The issue to be given special consideration in this article is how some of these swimmers dimensions and maximal oxygen uptakes adapted when the swimmers stopped regular training A more complete analysis of the data will be given elsewhere (7)

MATERIAL AND METHODS

The 30 girls studied in 1961 were re-examined in 1968/69 Measurements were also made in 1965 but these data will be reported on elsewhere (7) except for mean maximal oxygen uptake.

Their mean age was 22.2 (range 20—25) years in 1968. At the time for the last examination, most of the girls did not engage in any specific physical activity in their spare time. On an average five years (range 0—7) had elapsed since they stopped their regular training.

The same methods used in 1961 were used in 1968/69 i.e total hemoglobin using the alveolar CO method (12) heart volume in the supine position with biplane radiograms (10) and timed vital capacity with a spirometer (6) Maximal oxygen uptake was measured during work on a Krogh bicycle ergometer with a constant pedal rate of 50 rpm or an electrically braked ergometer[1] The levelling off criterion was used to establish maximal oxygen uptake. Expired air was collected in Douglas bags and gas samples were analyzed by the Haldane technique (2) Heart rate during work was recorded on an electrocardiograph. Lactate concentration was determined in blood drawn from a prewarmed finger tip and anlyzed according to the Barker & Summerson s method (4)

---

[1] Elema Schönander Stockholm

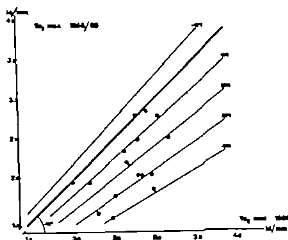


Fig 1 Individual values of maximal oxygen uptake in l/min 1969/69 as compared to 1961. The heavy line denotes 45° identification line and the thinner lines denote the deviation in per cent from the identification line. The square represents the girl who stopped swim-training just before the study

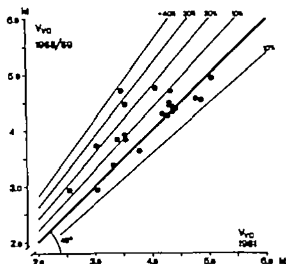


Fig 3. Individual values of vital capacity in former girl swimmers in 1968/69 as compared to 1961. For explanation of the lines see Fig 1

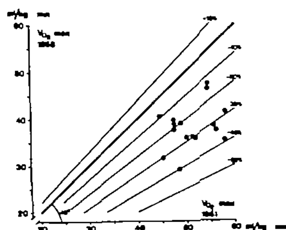


Fig 2 Individual values of maximal oxygen uptake per kg body weight in 1968/69 as compared to 1961. For explanation of the lines see Fig 1

RESULTS

The individual values in 1968/69 have been compared to corresponding values in 1961 and changes less than ±10 per cent have been disregarded.

Maximal oxygen uptake expressed in l/min decreased 10 to 40 per cent in twenty four girls, six of them more than 30 per cent (Fig 1). The oxygen uptake per kg body weight for the group displayed even greater changes (Fig 2) and the mean value for the group was reduced from 52 to 37 ml/kg×min. Ten of 30 girls had a decrease of more than 30 per cent.

The mean maximal heart rate was 199 beats/min in 1961 and 196 beats/min in 1968/69 ($p<0.05$). Mean blood lactate concentration was 11.8 mmoles/l in 1961 and 10.5 in 1968/69 ($p>0.05$). Vital capacity was unchanged in 19 of the girls, and the other ten demonstrated an increase which exceeded 40 per cent in one girl (Fig 3).

These latter girls also increased their body size the most during the period studied.

The individual changes in heart volume varied between +40 per cent and —20 per cent with no significant changes for the whole group when 1968 and 1961 were compared (Fig 4). Total hemoglobin, on the other hand, changed more strikingly displaying a mean reduction of 13 per cent ($p<0.05$). Fifteen girls showed a reduction of 10 to 30 per cent and only one girl demonstrated more than 10 per cent increase (Fig 5). She was the last one to stop swim-training.

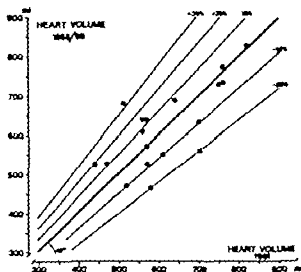


Fig 4 Individual values of heart volume in supine position in former girl swimmers in 1968/69 as compared to 1961 For explanation of the lines see Fig 1

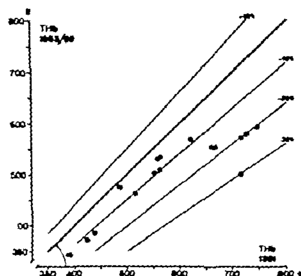


Fig 5 Individual values of total hemoglobin in former girl swimmers in 1968/69 as compared to 1961 For explanation of the lines see Fig 1

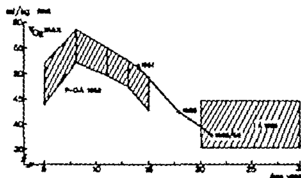


Fig 6. Mean maximal oxygen uptake per kg body weight in girl swimmers during a period of active training (1961) and 1965 and 1968/69 after stop of regular training. The left dashed area represents a material with ± 2 S D of normal females at 5—15 years of age (2) and the right a material of women 20—30 years of age (1)

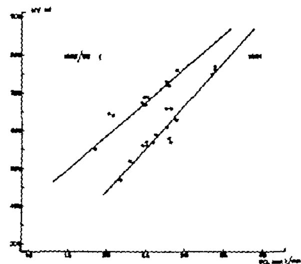


Fig 7 Individual values of heart volume and maximal oxygen uptake Unfilled symboles denotes values from 1961 with regression equation y=—13 46 +227.21× Filled symboles represent values from 1968/69 with regression equation y=230 8+178.35×

DISCUSSION

In this study of former girl swimmers, which was undertaken eight years after most of the girls were at the peak of their performance capability and on an average five years after they had stopped regular training, it was demonstrated that the most striking changes occurred in the functional capacity of the respiratory and circulatory system.

A comparison of the mean values for maximal oxygen uptake (ml/kg×min) in 1961 1965 and 1968/69 (Fig 6) with other materials in Sweden (1 2) makes these changes quite apparent. In 1961 the girl swimmers were 20 per cent better than relatively untrained girls (2) of the same age but 1968/69 5 per cent below the mean value found among 20—30 years old Swedish females (1)

Despite the striking decrease in maximal oxygen uptake, functional dimensions had not changed very much. Thus, heart volume was unchanged in the majority of the cases and still deviated from the normal relation to body surface area. In 1961 significant correlation was demonstrated between heart volume and maximal oxygen uptake. In 1968/69 there was still a good correlation between heart volume and maximal oxygen uptake but the regression line was significantly changed from that of 1961 (Fig 7) Similar results have been found in former male athletes (9) and still and former active middle-aged and old male athletes (11) Measurements of cardiac output and stroke volume in the latter material showed that the still active athletes when compared with young subjects, had a stroke volume which corresponded well to their heart volume. On the other hand, the former athletes had a lower stroke volume, during exercise than might be expected from their heart volume (Grimby and Saltin, unpublished data)

Vital capacity in 1961 was already enlarged in most of the girls in relation to their height. Against that background it is interesting to note that 1/3 of the girls increased their vital capacity even further. Some of them were still growing. The increase in vital capacity was especially true for those girls who continued with swim-training a few years after 1961 Swim-training then appears to cause an enlargement of the vital capacity a ariable which also remains more or less unchanged after the end of training. This has been confirmed in a longitudinal study of younger girl swimmers (5)

In contrast to the behavior of vital capacity and heart volume, total hemoglobin was reduced significantly in 1968 as compared to 1961 Thus, total hemoglobin is better related to the maximal oxygen uptake of the individual than to other dimensions of the cardio-respiratory system. Further analysis of the functional changes in relation to time of termination of training and age will be given elsewhere (7) The influence of varying length of time between stop of training and time for examination, and the actual age will be further analyzed.

SUMMARY

The thirty girls presented in Girl Swimmers (3) were re-examined in 1968/69 seven to eight years after their first examination and as a mean 5 years after they had stopped regular swimming. Those girls who had had very large maximal oxygen uptakes, heart volumes, vital capacities and total hemoglobin alues in relation to age and body size had changed strikingly Their mean maximal oxygen uptake was reduced from 52 to 37 ml/kg×min. The latter value is below the mean value found in untrained Swedish females of the same age but within ±2 S.D Their heart and lung volumes were not altered significantly but mean total hemoglobin had decreased by 13 % In 1961 good cor relations were found among cardio-respiratory variables studied, but this was not the case in the 1968/69 study The influence of varying length of time between stop of training and time for examination and the actual age will be further analyzed.

ACKNOWLEDGEMENT

This study was supported by grants from the Swedish Medical Research Council (project No. 19X 2031)

REFERENCES

1 Astrand, L. Aerobic work capacity in men and women ith special reference to ge. *Acta Physiol Scand, 49* Suppl 169 1960.

2 Astrand, P-O *Experimental studie f physical orking capacity relation to age and sex.* Munksgaard, Copenhagen, 1952.

3 Astrand, P-O., Engström, L., Eriksson, B. O Karlberg, P Nylander, I., Saltin, B and Thorén, C. *Girl immers. Acta Paediat Scand* Suppl 147 1963

4. Barker, S. B., and Summerson, W H The colorimetric determination of lactic acid in biological material. *J Biol Chem* 138: 535, 1941

5 Engström, I., Eriksson, B. O Karlberg, P Saltin, B., and Thorén, C., Preliminary report on the development of lung volumes in young girl swimmers. *Acta Paediat Scand* Suppl. 217 73 1971.

6. Engström, I Karlberg, P and C Swartz, C., Respiratory studies in children. IX. Relationship between mechanical properties of the lungs, lung ol-

umes and entilatory capacity I healthy children. 7—15 years of age. *Acta Paediat Scand 51* 68, 1962.
7 Eriksson, B O Engstrom, L, Karlberg, P Saltin B and Thorén, C. Changes in circulatory and respiratory dimensions and maximal oxygen uptake in former girl swimmers after stop of regular training. T be published.
8. Grimby G Nilsson, N J and Saltin, B Cardiac output during submaximal and maximal exercise in activ middle-aged athletes. *J Appl Phy iol 21* 1150, 1966.
9 Holmgren, A., and Strandell, T The relationship between heart volume total hemoglobin and physical working capacity in former athletes. *Acta Med Scand 163* 149 1959
10 Kjellberg, S. R., Rudhe, U and Sjostrand, T The relation of the cardiac volume to the weight and surface f the body the blood volume and the physical capacity for work. *Acta Radiol 31* 113, 1949
11 Saltin, B and Grimby G. Physiological analysis of middleaged and old former athletes. Comparison with still active athletes of the same age. *Circulation 38:* 1104, 1968
12 Sjostrand, T A method for the determination of the total hemoglobin content of the body *Acta Physiol Sc nd 16.* 211 1948.

K y words Girl-swimmers, V_{O_2} max, heart volume, total hemoglobin, vitalcapacity f llow up.

(B.E.) S:t Görans Childrens Hospital
Box 12500
S-112 81 Stockholm
Sweden

Acta Paediat Scand Suppl 217 1971

PRELIMINARY REPORT ON THE DEVELOPMENT OF LUNG VOLUMES IN YOUNG GIRL SWIMMERS

INGA ENGSTROM, BENGT O ERIKSSON PETTER KARLBERG BENGT SALTIN and CLAES THOREN

From the Department of Pediatrics of Karolinska Institutet at Karolinska Hospital and St Gorans Hospital Stockholm Department of Pediatrics University of Göteborg and Department of Physiology Gymnastik och Idrottshögskolan, Stockholm Sweden

INTRODUCTION

In competitive swimming for women top results are often achieved by girls no more than 15—16 years of age. In a cross sectional study of the functional dimensions of 30 girl swimmers from 12—16 years, it was found than many girls in this young age group could be trained to an exceptionally high functional capacity which was more related to the degree of training than to age and body size (1) These were the final results of several years of hard training, and the possible contribution of constitutional factors to the results could not be excluded.

In order to further elucidate the pattern of development of functional dimensions during hard physical training, a longitudinal study of a group of young girls at the beginning of their swim training was started in 1963 Lung volumes, heart volume, total hemoglobin, blood volume and maximal oxygen uptake were measured at regular intervals up to the age of 16. The study is still in progress. Preliminary lung volume results during training will be presented here.

MATERIAL AND METHODS

Twenty nine girls were studied at the beginning of their training period and followed with examinations once a year up to the age of 16. In sixteen of the girls the two first examinations were performed at an interval of only 1/2 a year At the start of the study the girls were between 9 and 13 years, with a mean age of 11 1/2 years. Twenty of the girls had reached the age of 16 years in 1969 Before the start of the study the mean duration of training in the group was 2 years with a range from 0—5 years. Nineteen of the girls had trained 2 years or less. During the period 1963—1969 sixteen girls ceased training.

The lung volumes were measured by using the closed circuit Helium dilution method, and the norms for healthy children in the same age range were used for comparison (3) Height and other anthropometric measurements were obtained at each examination.

RESULTS

In Figs 1 and 2 functional residual capacity total lung volume and vital capacity are presented longitudinally in relation to height in diagrams with the mean ±2 S.D for healthy children (3) It is evident from the diagrams that the majority of values for functional residual capacity and total lung capacity are scattered within the 2 S.D limits for healthy children, only a few values gradually increasing above +2 S.D As regards vital capacity the tendency to increase volume is more apparent with an upward direction of the lines.

Supported by a grant from Statens Medicinska Forskningsråd, project No 19X 2051

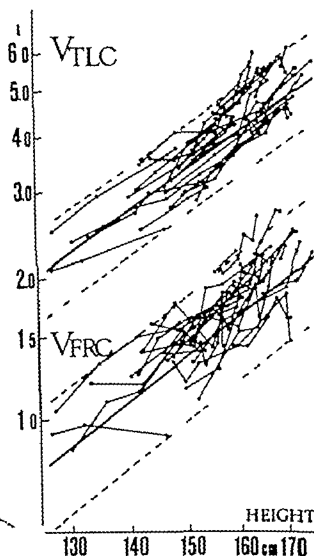


Fig. 1 Total lung capacity (V_{TLC}) and functional residual capacity (V_{FRC}) relation to height for each individual girl. The regression lines for means and 2 SD for healthy children are drawn.

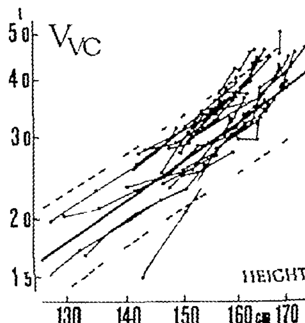


Fig. 2 Vital capacity (V_{VC}) in relation to height for each individual girl. The regression line and 2 SD for healthy children are drawn.

For the statistical analyses we used the individual deviation from the regression line for each variable, expressed as a fraction of standard deviation, in order to eliminate the influence of the normal relationship between growth of the lungs and body growth as a whole.

Lung volumes were analysed cross sectionally at the first examination and at the last examination, Table 1. The time interval between the two examinations ranged between one and five years with a mean of 3.6 years. At the first examination vital capacity in the group had not increased significantly but had done so significantly at the final examination. Total lung capacity and functional residual capacity were already significantly larger than normal at the first examination but did not increase further in relation to height during the period of study.

The material was stratified into two groups according to duration and degree of training before the first examination, Table 2. It was then found that in the group comprising the girls who had been training one year or more, three or more times a week, mean lung volumes were significantly greater than normal, whereas in the group comprising the girls who had been training less

Table 1. Lung volumes of the 29 girls ... examined the beginning of the training and 1—5 years later. Deviation in fraction of SD of normal values.

	first test	last test	difference
V	+0 37±0 22	+0 93±0 22	+0.34±0.07**
V_{TLC}	+0 49±0 18	+0 77±0.24	+0.27±0.17
V_{FRC}	+0 73±0 15 **	+0 99±0 20	+0 05±0.23

Significance ... = p < 0 001 ... = p < 0.01

Table .. Lu g olume grl mm s at the first xamination accord g to d gr f trai g Deviation in fractio S.D f normal alues.

			Mean ± S E
$V_{\backslash}$	tr_ined	18	+0 62 ± 0 23
\	non trained	11	−0 04 ± 0.12
V_{TLO}	trained	18	+1.02 ± 0.31**
V_{TLO}	non trained	11	+0 17 ± 0.3
V_{FRO}	trained	18	+0.71 ± 0.19
V_{FRC}	non trained	11	+0 68 ± 0 32

trained = 1 year 3 times eek
Significance =$p < 0\ 01$, =$p < 0\ 05$

than one year or not at all, mean lung volumes did not deviate significantly from normal values.

In the 16 girls who were studied at 6 month intervals at the beginning of their training period, vital capacity increased significantly more ($p < 0.05$) than expected during these 6 months in relation to the height increment during the same period.

The increase in lung volumes was further analyzed during the period or rapid growth between 12 and 14 years, Table 3 The mean increase in heigth was 10 cm, and all the girls had menarche in the middle of this period.Vital capacity increased significantly more than expected in the 12 girls who trained during this period in relation to the increase in height, whereas vital capacity in the 6 girls who were not training during this period did *not increase more than* expected in relation to the increase in height. No similar difference between the two groups could be found as regards functional residual capacity or total lung capacity

COMMENTS

Preliminary analyses of the increase in lung volumes during swim training showed that the girls had larger lung volumes than normal after period of training, thus confirming the results found in a previous cross sectional study of girl swimmer (1)

Lung olume increases at the beginning of the training period which s most evident n respect to total lung capacity and functional residual capacity

However during continued training, there is

Table 3. In ase in ital pacity in f actions of S.D in g l mm bet en ag 12 and 14

		Mean ± S E
training	12	+0 62 ± 0.11
non training	6	+0.20 ± 0.15
difference between means $p < 0.001$		

primarily an increase in vital capacity which is disproportional to growth in height as well as to total lung capacity This is apparent during only a 6 months period of training and unquestionable in the period of rapid growth during puberty The effect on vital capacity of swim training is in conformity with the observations of Ekblom (2) of a small group of 11 year old boys exposed to physical training

The steady increase in vital capacity during continued training without corresponding increase in total lung capacity points to functional growth rather than anatomical growth. A change in breathing pattern as a result of training or an increase in muscular strength, making it possible for the girls to use their full capacity to exhale forcibly may be possible explanations.

This will be discussed further in connection with presentation of all the functional dimensions stud ied longitudinally All observations up to age of 16 years will then be available for all the girls.

SUMMARY

Preliminary results of an increase in lung volumes during swim training from a longitudinal study of 29 girl swimmers during the first years of training up to the age of 16 are presented. The study is still in progress, as only 20 of the girls have reached age 16. Static lung volumes were found to be larger than normal after only a few years of training and only increased further in relation to the increase in height. Vital capacity increased during continued training to a significantly greater extent than expected with regard to the normal growth in height. Some evidence was found of a relationship between the degree and duration of training and the increase in vital capacity a matter wich will be analysed further when all the girls have reached age 16.

REFERENCES

1. Astrand, P. O., Engström, L., Eriksson, B. O., Karlberg, P., Nylander, I., Saltin, B. and Thorén, C.: Girl Swimmers. *Acta Paediat Scand* Suppl. 147, 1963.

2. Ekblom, B.: Effect of physical training on oxygen transport system in man. *Acta Physiol Scand* Suppl. 328, 1969.

3. Engström, I., Karlberg, P. and Swarts, C.: Respiratory studies in children. IX. Relationship between mechanical properties of the lungs, lung volumes and ventilatory capacity in healthy children 7—15 years of age. *Acta Paed Scand* 51: 68, 1962.

Key words: swim training, girls, lung volumes, longitudinal study

(I.E.) Department of Pediatrics
Karolinska Hospital
S-104 01 Stockholm, Sweden

INVESTIGATIONS OF THE PHYSICAL WORKING CAPACITY OF OBESE CHILDREN

R. MOCELLIN and J. RUTENFRANZ

From Institut für Arbeitsmedizin der Justus Liebig-Universität Giessen, Germany

About 10 years ago we observed that obese children displaying shortness of breath when climbing stairs and a general decrease in physical work capacity were consulting the pediatric out-patient clinic with increasing frequency. Because of this symptomatology the majority of these children did not take part in physical exercise. We usually found that these children were overweight by more than 40 % of the normal in relation to height and had a substantially reduced physical work capacity. At the same time Adams *et al.* (1) reported a decline in the physical working capacity of 24 obese 9-year old boys. In a book about the problem of obesity in children, Börjesson confirmed this finding in 26 boys with an average age of 8.8 years and pointed out that this reduction in the physical work capacity existed in relation to body weight as well as with regard to total hemoglobin and heart volume.

Because obesity is a condition which does not arise suddenly but develops slowly it is of some importance to know whether the decline in physical work capacity develops continuously in step with overweight or whether the decline is only measurable when overweight has attained a certain level.

MATERIALS

In order to shed more light on this question not only the obese patients were included in our investigation healthy children with body weight increase of more than 10 % of the body weight corresponding to their heights also participated. In this way we obtained a population of 102 children aged 8 to 18. 37 were girls and 65 were boys. The investigation began in 1958 and ended in 1968.

METHODS

Overweight was determined by means of somatograms (3) and expressed in percent of the body weight which could be expected on the basis of height.

We determined physical work capacity as W_{170} according to a method, previously described by us (4) which differs from the usual method and yields higher values. The method was standardized on several hundred boys and girls for age, body weight and height parameters.

RESULTS

The height of the children and adolescents examined by us corresponded to the age norm ±2 %. The children's body weight was elevated by ca. 31.9 % ±14.3 % in relation to the predicted body weight. The percentage of overweight was less in the older children (15—18 years = 22.7 %) than in the younger ones (36.2 % from 8 to 11 years). For our further considerations it seemed to be important to take into account the physical working capacity of the children in relation to both age and physical development. As is

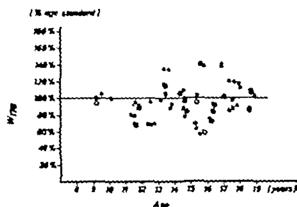


Fig. 1 W_{170} (% of age standard) related to age in 102 obese (boys, o <40 % • >40 % overweight, and girls with double-outlined symbols.

well known, W_{170} in relation to age makes it possible to establish whether or not a child differs its age group in respect to physical performance capacity

Relating W_{170} to physical development provides information on whether or not a child's cardio-respiratory system is in accordance with the development of the organism. Fig 1 represents the children's physical work capacity calculated as percent of the age norm. According to the Figure children's W_{170} varied ca. ±40 % around the values, irrespective of age and overweight. Thus, neither a positive nor a negative relation

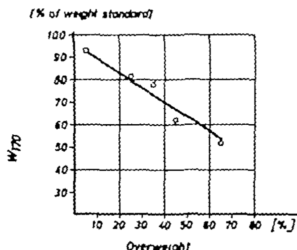


Fig 3 W_{170} (% of weight standard) related to overweight in obese children and adolescents Symbol as in Fig. 1

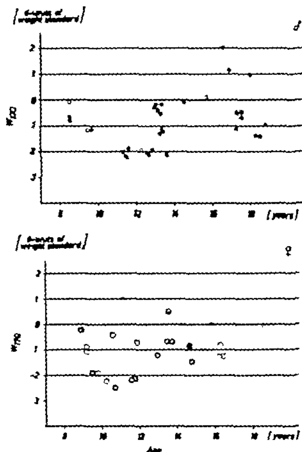


Fig. 2 W_{170} (S.D units of weight standard) related to age in 65 obese boys and 37 obese girls.
Fig. 2.

between age norm and physical work capacity could be observed. By relating the children's physical work capacity to their body weight, a wholly different picture was obtained.

As can be seen in Fig. 2, the children's physical work capacity with the exception of 6 boys and 5 girls, was now less than the mean value for the related weight standard. Moreover it is worth mentioning that almost all boys who were overweight by more than 40 % displayed a physical work capacity under the S.D level. Girls overweight by more than an average of 40 % also displayed pronounced decline in work capacity But there were still some patients whose physical work capacity lay within the S.D area. Because of this finding, it seemed reasonable to relate the decrease in physical work capacity (in percent of weight standard) to overweight.

As shown in Fig. 3, we found a linear decline in the relationship between work capacity and body weight.

CONCLUSION

From our investigations it, thus, follows that the decrease in physical work capacity develops gradually in relation to increasing overweight. Therefore, each degree of overweight requires its own particular training program if the object is to maintain equilibrium between cardio-respiratory performance capacity and body weight.

REFERENCES

1. Adams, F. H., Bengtsson, E., Berven, H., Börjeson, M., Engström, I., Ikkos, D., Jonsson, B., Karlberg, P. and Kraepelin, S.: Determination by means of a bicycle ergometer of the physical working capacity in children. *Acta Paediat Scand*, Suppl. *118*: 120, 1959

2. Börjeson, M.: Overweight children. *Acta Paediat Scand* Suppl. 132, 1962.

3. Hellbrugge, Th., und Vogt, D.: Zur Beurteilung des Wachstumszustandes mit Hilfe von Somatogrammen. In Th. Hellbrugge (ed.) *Vorsorgeuntersuchungen bei Jugendlichen* Deutscher Ärzteverlag o. J. Köln—Berlin 1960, p. 70.

4. Mocellin, R., Lindemann, H., Rutenfranz, J. and Sbresny, W.: Determination of W_{170} and maximal oxygen uptake in children by different methods. *Acta Paediat Scand* Suppl. 217:13, 1971

Key words: Working capacity obesity

(R.M.) Universitäts Kinderklinik
8 München 15 Lindwurmstr. 4
Germany

BODY COMPOSITION AND FITNESS IN OBESE CHILDREN BEFORE AND AFTER SPECIAL TREATMENT

J PARIZKOVA, M. VANECKOVA, S. SPRYNAROVA and M. VAMBEROVA

From the Institute of Physical Culture Research, Prague, Czechoslovakia

In childhood and adolescence the diagnosis of obesity especially in its initial stages, is substantially more difficult and simultaneously more important than in adults when using usual height weight standards only The degree of sexual maturation, the intensity of physical activity influencing the development of muscle mass etc. have a profound impact on the height weight ratio (4) Therefore, a more thorough evaluation of somatic development with respect to body composition, (i.e. lean body mass/LBM/ and fat proportions 7 9) related to a child's functional development (6) is indispensable.

MATERIAL AND METHODS

A study of the somatic and functional development of obese children, who regularly attended the outpatient department of children's clinic in Prague (16) was performed. Since the number of children with abnormalities in endocrine activity revealed by routine clinical and laboratory examinations, was negligible, only children with diagnosed hyperalimentary obesity were included in our groups (22) The onset of puberty in older children was normal physical activity was low as compared to normal children Children of approximately the same age and duration of obesity were selected, thereby necessarily limiting the number of subjects in our groups

As regards somatic characteristics the increased body weight in obese children is not only due to enhanced deposition of fat (displayed in a manner reminiscent of an adult woman with maxima over the hips and abdomen—3) but to increased lean body weight as well as established by densitometry (Table 1 16 18) Bicristal breadth was significantly greater in the obese boys than in normal boys. The findings mentioned cannot be explained by fat deposition over the hips, as fat layers, measured as skinfolds, do not correspond to the absolute difference in pelvic breadth (18) This difference was not found between obese and normal girls. Corresponding results were found in further groups of obese boys aged 11 (n=9) 12 (n=14) and 13 years (n=10)—excess fat runs parallel to absolute and relative pelvic broadness (bicristal breadth)

When the generally sturdier constitution (greater LBM, broader pelvis and femoral condyle breadth, greater circumferential measures /Table II/) occurs in conjunction with excess fat, some abnormality in somatotrophin (STH) secretion may be considered. But as subject stature was mostly normal and skiagraphs of the skull (sella turcica) were negative this abnormality was not indicated in our children

As regards functional characteristics, aerobic capacity with both a maximal and standard work load was studied. Comparison of a group of obese boys of approximately the same age and duration

Table 1 *Anthropometric measures and body composition in normal and obese boys and girls (13—14 years)*

		Height cm	Weight kg	Fat %	LBM kg	Leg Length cm	Biacrom. cm	Bicrist. cm	Bitroch. cm
Boys Normal (n=28)	Mean	161.8	50.4	12.5	43.9	100.2	34.4	22.8	[illegible]9.5
	SD	6.3	6.7	5.9	5.1	4.2	1.6	1.8	2.4
Obese (n=12)	Mean	161.2	68.9	29.5	48.6	99.9	33.8	27.7	30.5
	SD	2.1	6.9	3.2	5.0	3.1	1.4	1.0	1.9
Girls Normal (n=25)	Mean	156.9	50.4	18.1	40.3	—	34.6	26.8	—
	SD	5.7	10.7	6.0	4.9	—	2.6	2.3	—
Obese (=9)	Mean	157.5	68.9	31.9	46.7	95.8	32.0	27.4	31.5
	SD	4.0	10.2	3.7	6.4	3.1	2.0	1.1	2.1

of obesity (mean age 11.8 years, n=7) with a group of normal boys of the same age (n=21) confirmed the differences in somatic development mentioned (increased body weight due to increased fat as well as lightly increased lean body mass and height—Fig. 1). The comparison also showed the same absolute value for maximal oxygen uptake, measured during gradually increasing workloads on a horizontal tread-mill up to the point of subject exhaustion. Nevertheless, maximal O_2 uptake in the obese was achieved after a shorter period of running and at lower speeds. Maximal oxygen uptake, as related to total and lean body weight, was significantly lower in the obese (Fig. 1). Excess fat obviously had an important impact on physical efficiency.

The same conclusions can be drawn from the data of a simple steptest which was performed e.g. on a group of Tunisian boys aged 1 (n=29) and 12 years (n=100) (5). fat correlated positively to the increase in pulse rate during the recovery period and negatively to the steptest index. The higher the proportion of fat, the poorer the results, as regards physical fitness characterised by the steptest the reverse applies to LBM.

Thus obese children are morphologically characterised by increased fat, lean body mass, typical body build and by limited fitness and poorer work economy as proved by further longitudinal observations during reduction treatment. Inactivity which is both primary and secondary due to the morphological characteristics mentioned is said to be one of the most important causes of obesity during growth, as almost no pronounced increase in energy input can be proved (1, 2, 3, 4). Physical exercise, is therefore, often used for reduction so as to increase energy output and to prevent the breakdown of lean body weight, observed mainly when only a sharp decrease in caloric input is used for reduction. A temporary decline in height increments occurred in children when caloric input was lowered to 1000 Cal/day (22). A com

Table 2 *Anthropometric measures in normal and obese boys (13—14 years)* Values in cm.

		Chest depth	Chest breadth	Chest circumference insp.	Chest circumference exp.	Circumference arm	Circumference forearm	Circumference calf	femur breadth
Normal	Mean	16.9	22.8	81.5	73.4	23.1	[illegible]3.1	22.4	9.6
	SD	3.7	1.5	4.6	4.5	1.2	1.2	2.0	0
Obese	Mean	18.2	26.1	97.8	88.3	27.6	25.6	37.6	10.1
	SD	1.9	2.4	3.9	4.5	2.5	1.1	1.6	

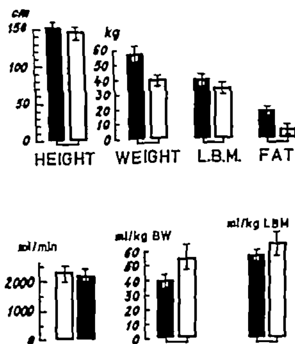


Fig. 1 Comparison of height, weight, body composition and maximal oxygen uptake in obese (=7 and normal (n=21) boys. Dark areas=obese.

plex therapy consisting of exercise, controlled diet and an instructional program seems to be most suitable for the obese during their growth period, as weight reduction is considered to be contrary to natural growth tendencies and growing up to adequate height while preserving the current weight is recommended (3 4) However weight reduction is necessary in extreme cases. Therefore, an experimental therapy based on the factors mentioned (19) was utilised for severe cases and results followed longitudinally (13 16)

Selected obese children regularly visiting the outpatient department spent seven to eight weeks in a special summer camp the controlled diet provided 1700 Cal/day with restricted carbohydrates and fats but ample protein of all types, as well as fruit and vegetables. Maximal fluid intake was 1500 ml per day Most important was an intensive program of physical activities including all suitable types of physical exercises (15 16, 22) *Children were occupied the entire day with two-hour break after lunch.* Finally an instructional program sought to modify improper nutrition and activity patterns and to replace them with a sound approach to physical activity including sufficient outdoors program. The results of this therapy was controlled by means of direct measurements of body composition changes by means of densitometry and tests of physical fitness (16, 17 20)

RESULTS AND DISCUSSION

Repeated measurements of oxygen uptake of standard work load (i.e. one sixth of the maximal work load—2) on a bicycle ergometer before and after weight reduction in a group of 18 obese boys and 15 obese girls (mean age 12.6 years) showed significant decrease in oxygen uptake and ventilation rate, both in absolute terms and related to total and lean body weight (Table III) Pulse

Table 3 *Weight per cent of LBM, oxygen uptake, ventilation and vital capacity in obese boys and girls before and after reduction*

	Boys (n=18)				Girls (n=15)			
	before reduction		after reduction		before reduction		after reduction	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Weight, kg	65 73	3 46	58 52	2 82	70 33	2 85	65 13	2 35
LBM, %	68 6	0 97	74 8	1 14	68 1	0 95	72 9	1 01
V_{O2} ml	770	30	570	30	730	50	620	80
V_{O2} ml/kgBW	11 6	0 2	9 7	0 4	10 2	2 0	9 7	[illegible]
V_{O2}, ml/kg LBM	17 2	0 3	12 9	0 06	15 4	1 0	13 3	0 2
V_E L	15 74	0 59	13 26	0 60	15 48	0 65	15 0	0 77
V_E/kgLBM	0 34	0 01	0 29	0 00	0 34	0 02	0.32	0 01
VC, ml	2942	105	3073	115	2640	124 8	2838	133 8

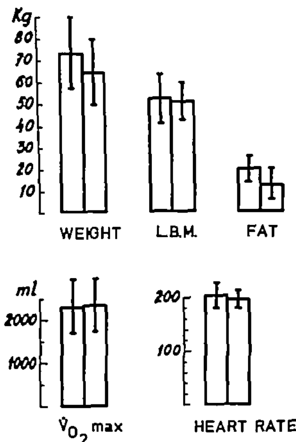


Fig 2 Comparison of eight, body composition, maximal oxygen uptake and heart rate in group of obese before and after reduction.

rate also decreased significantly both during and after the work load (10) These changes indicate decrease in caloric output and decreased energy demands for the same work load after reduction of excess fat children performed the same work load with smaller caloric outputs than before reduction. Vital capacity (Table III) and muscle force also increased in these children after reduction (23) and their blood cholesterol levels decreased significantly (12) thus latter change was only significant in boys, however

The adaptation to increased physical activity resulting in a decrease in body fat and improved fitness due to the stay in summer camp, also manifested itself in some changes in the blood levels of fat metabolism indicators before and after maximal work load After reduction, the initial values of non-esterified fatty acids (NEFA) decreased significantly (1 17 to 0.63 m Eq/l) before reduction their alues significantly decreased during work (1 00 m Eq/l) and did not change after a 10 minutes rest. After weight reduction NEFA remained the same during exercise and increased significantly after rest to 0.83 m Eq/l, thus obviously manifesting an increased ability to release NEFA from adipose tissue into the blood stream as fuel for muscular work (14) Blood levels of esterified fatty acids and glucose did not change significantly as a result of weight reduction.

Repeated measurements of maximal oxygen uptake before and after reduction showed unchanged absolute values in four boys reduced for the first time at the mean age of 14.5 years. Body weight was decreased through reduction of fat a slight decrease in LBM was not significant (Fig. 2) Maximal heart rate and oxygen pulse did not change either The mean LBM in % or body weight increased from 72.2 to 81.8 % and fat decreased from 27 1 to 8.1 % Previous measurement made in seven obese boys even showed a decrease in maximal oxygen uptake (20) In both studies, however, maximal oxygen uptake after weight reduction was achieved after longer runs at higher speeds than before reduction.

Another small group of obese boys, who got special treatment repeatedly for four successive summer camps was studied (n=4, initial age 11.8 years) These boys were especially severe cases of obesity the family history of almost all the children disclosed obesity or a tendency to it, in at least one parent, grandparent or sibling. Biliary disease, diabetes, arteriosclerosis, hypertension etc. were also fairly common in their families. Apart from the common diseases of childhood, none of the children had had any serious illness, but they had been markedly obese from early childhood. Height did not differ significantly from Tanner's standards (Fig. 3) Body weight was considerably higher than the standards and did not normalise completely even after marked reductions (Fig. 3) During the normal school year when these children wer only treated in the outpatient department,

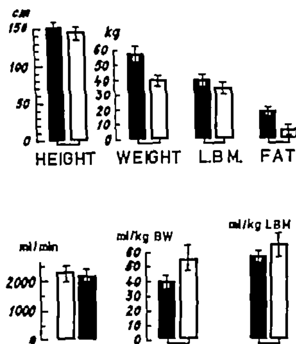


Fig. 1 Comparison of height, weight, body composition and maximal oxygen uptake in obese (n=7 and normal (=21) boys Dark areas=obese.

plex therapy consisting of exercise, controlled diet and an instructional program seems to be most suitable for the obese during their growth period, as weight reduction is considered to be contrary to natural growth tendencies and growing up to adequate height while preserving the current weight is recommended (3 4) However weight reduction is necessary in extreme cases. Therefore, an experimental therapy based on the factors mentioned (19) was utilised for severe cases and results followed longitudinally (13 16)

Selected obese children regularly visiting the outpatient department spent seven to eight weeks in a special summer camp the controlled diet provided 1700 Cal/day with restricted carbohydrates and fats but ample protein of all types, as well as fruit and vegetables. Maximal fluid intake was 1500 ml per day Most important was an intensive program of physical activities including all suitable types of physical exercises (15 16, 22) Children were occupied the entire day with two-hour break after lunch. Finally an instructional program sought to modify improper nutrition and activity patterns and to replace them with a sound approach to physical activity including sufficient outdoors program. The results of this therapy was controlled by means of direct measurements of body composition changes by means of densitometry and tests of physical fitness (16, 17 20)

RESULTS AND DISCUSSION

Repeated measurements of oxygen uptake of standard work load (i.e. one sixth of the maximal work load—2) on a bicycle ergometer before and after weight reduction in a group of 18 obese boys and 15 obese girls (mean age 12.6 years) showed significant decrease in oxygen uptake and ventilation rate, both in absolute terms and related to total and lean body weight (Table III) Pulse

Table 3 *Weight per cent of LBM, oxygen uptake ventilation and vital capacity in obese boys and girls before and after reduction*

	Boys (n=18)				Girls (n=15)			
	before reduction		after reduction		before reduction		after reduction	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Weight, kg	65 75	3 26	58 32	2 82	70.33	2.85	63.13	2.35
LBM, %	68 6	0 97	74 8	1 14	68 1	0.95	72.9	1 01
V_{O_2} ml	770	30	570	30	730	50	620	80
V_{O_2} ml/kgBW	11 6	0 2	9 7	0 4	10	2.0	9 7	2 0
V_{O_2}, ml/kg LBM	17 2	0 5	12 9	0.06	15 4	1 0	13.3	0.2
$\dot{V}$ L	15 74	0 59	13 26	0 60	15 48	0 65	15.0	0.77
V_L/kgLBM	0 35	0 01	0 29	0 00	0 34	0 02	0.32	0 01
VC, ml	2942	105	3073	115	640	124 8	2838	133 8

CONCLUSION

Obese children are characterised, in addition to increased weight and fat, by greater lean body mass and sometimes greater skeletal robustness, as well as by a special body build, i.e. a broader pelvis. Oxygen uptake with maximal work loads did not differ from that of normal children of the same age, but was achieved after a more modest performance. In the obese with large fat deposits, the same maximal oxygen uptake was found after shorter run at lower speed than was the case for normal children (or in the obese after reduction of weight) after longer run at greater tread-mill speed with smaller fat deposits. Greater work economy after reduction of weight and fat was also proved by reduced oxygen uptake, ventilation, pulse rate etc. at the same standard work load. Better results with weight reduction are achieved in smaller children before puberty reduction is more difficult later, causes LBM decrease and functional improvements are poorer The prevention and reliable diagnosis of early stages of obesity by controlling body composition and functional capacity seems, therefore, indispensable to child health care.

REFERENCES

1 Broch, H. Obesity in childhood, physical growth and development of obese children. *Amer J Dis Child* 58 457 1939
2. Janda, F Suitability of physical work with regard to the development of children and adolescents *Rev Czech Med* 9 82, 1963.
3 Mayer, J The physiological basis of adiposity and leanness *Nutr Abstr Rev* 25 597 1955.
— Obesity in adolescence. *Med Clin North Am* 49 421 1965
5 Merhautová, J & Pařízková, J Développement somatique et fonctionnel chez les enfants tunisiens *J Physiol* (Paris) In press.
6 Mocellin, R & Rutenfranz, J Untersuchungen uber die körperliche Leistungsfähigkeit gesunder und Kranker Heranwachsender *Zts kr Kinderheil* 104 179 1968
7 Pařízková, J The measurement of lean body mass in adolescents by hydrostatic weighing method. *Cs Fysiol* 8 426, 1959
8 — The development of subcutaneous fat in normal and obese children *Physiol Bohemoslov* 9 253, 1960
9 — Age trends in fatness in normal and obese children. *J Appl Physiol* 16 173, 1961
10. — Vaněčková, M. & Vamberová, M. A study of changes in some functional indicators following reduction of excessive fat in obese children *Physiol Bohemoslo* 11 351, 1962.
11. — Vamberová, M. Modification des graisse de réserv pendant différentes periodes de la cure de dé maigrissement chez les enfants obèses. *Diet Nutr* 12 31 1961
12 — Vamberová, M Opplt, J & Vaněčková, M.. The development of adipose tissue in man and its relationship to some functional indicators. *Czech Acad Sci Praha*, p 66, 1963
13. — Physical activity and body composition. *Proc Soc Study Hum Biol* London 1965 Pergamon Press, Oxford 1965 p. 161
14. — Stanková, L., Sprynarová, S. & Vamberová, M.. Influence de l exercise physique sur certains index métaboliques sanguins chez les garçons obèses après l'effort. *Nutr Diet* 7 21, 1965
15. — Nutrition and its relation to body composition in exercise. *Proc Nutr Soc* 25 93 1966.
16. — & Vamberová, M. Body composition as criterion of the suitability of the reducing regimen in obese children. *Dev Med Child Neurol* 9 202, 1967
17 — Compositional growth in relation to metabolic activity XII. *Inter Cong Ped* Mexico 1968. Opening plenary session. P 32.
18 — Body fat and body build in normal and obese boys. Symposium Anthropological Aspects of Human Growth *VIIIth Inter Cong Anthrop Ethnol Sci* Tokyo-Kyoto 1968.
19 — Nutrition, body fat and physical fitness. Borden *Rev Nutr Res* 29 1968.
20. Sprynarová, S. & Pařízková, J Changes in the aerobic capacity and body composition in obese boys. *J Appl Physiol* 20 934, 1965.
21. Tanner, J M., Whitehouse, R. G & Takaishi, M.: Standards from birth to maturity of height, weight, height velocity and weight velocity British children 1965 *Arch Dis Child* 41 454 and 613 1966.
22. Vamberová, M. Therapeutic regimen in obese children. *Rev Czech Med* 4 135 1958.
23. Vaněčková, M Vamberová, M. A study of changes in some functional indicators following reduction of excessive fat in obese children. *Physiol Bohemoslo* 11 351, 1958.

(J P) VYZKUMNY USTAV TELOVYCHOVNY
Praha 1 Ujezd 450 Czechoslovakia

Keyword Obese girls and boys, body composition, anthropometric measures, oxygen consumption, physical training.

CIRCULATORY AND RESPIRATORY DIMENSIONS AND FUNCTIONAL CAPACITY IN BOYS AGED 8—13 YEARS WITH BRONCHIAL ASTHMA

STURE BEVEGÅRD BENGT O ERIKSSON, VIGGO GRAFF LONNEVIG, SVEN KRAEPELIEN and BENGT SALTIN

From the Allergy Department Sachs' Children's Hospital the Department of Clinical Physiology Södersjukhuset and the Department of Physiology Gymnastik och Idrottshögskolan Stockholm Sweden

Bronchial asthma is the most frequent chronic disease in childhood. The morbidity in Sweden is about 1.5 % Children with asthma, overweight, diabetes or congenital heart disease are often regularly excluded from physical training. In asthmatic children, the reason may be that physical exercise often induces athmalike attacks (4, 7 13) and also that parents and teachers restrict the physical activity of their children because of an over protective tude. Furthermore, these children may become physically inactive for fear of inducing breathing disturbances.

In the literature there are only a few investigations of the effect of physical training of asthmatic children (7 10, 11 14 16) and there are no systematic studies indicating that these children should be more generally excluded from physical training Investigations of the effect of physical training on asthmatic children speak in favor of clinical improvement (6, 7 11 16) In previous studies it is mostly the respiratory function that has been measured and circulatory dimensions have not usually been evaluated. It is possible that physical inactivity can retard the development of the circulatory system and that this as well as impaired pulmonary function may influence the children's physical capacity The present investigation is an attempt to further elucidate this problem

Table 1 *Classification of 20 boys with asthma* (Kraepelien et al 1958)

	Group	No. of cases
Mild asthma with less than 5 shorts attacks during 1969	I	3
Moderatly severe asthma with 5—10 attacks during 1969	II	7
Severe asthma with more than 10 attacks during 1969	III	10
	20	Total

MATERIAL AND METHODS

The material consists of twenty boys aged 8—13 years from the department of allergy at the Sachs Children's Hospital in Stockholm. The upper age limit is 13 years in order to avoid interference with puberty With respect to height all boys but one were within two standard deviations of the normal value for Swedish boys (3)

The material is divided into three groups according to the degree of severity of asthma (Table 1) (9) The material consists mainly of advanced cases and six children were on steroid therapy At the time of investigation all boys were clinically free of symptoms and showed no signs of infection.

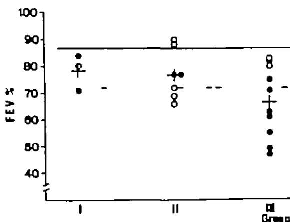


Fig. 1 FEV % in relation to clinical severity of bronchial asthma in 20 boys. The classification of the three groups is given in Table 1 Crosses denote erage alues for the groups and filled circles denote subjects who got asthmalike attacks during exertion Solid denotes normal alue and dotted line —2 S.D

Symptomatic drugs were excluded twelve hours before the tests. The in estigation took place during the period *January—March 1970*

Static lung olumes were measured in a spirometer with determination of functional residual capacity by a closed helium system. Dynamic lung function was measured with a Bernstein spirometer. Blood gas analysis were performed on arterialized capillary blood using a pH/gas analyzer (I I model 113) Heart volume was measured in the prone position by two-plane roentgenograms (8) The total amount of hemoglobin (THb) was deter mined with the alveolar CO-method (16) and blood volume was calculated using the hemoglobin concentration of finger blood.

Exercise tolerance tests, using an electrically braked bicycle ergometer were performed on two consecutive days. For determination of oxygen uptake during submaximal and maximal work expired air was collected in Douglas bags and analyzed ac cording to a microtechnic of the Scholander method. The criterion of the oxygen uptake ha ing reached the maximal level was that a rise in th intensity of the work did not increase the oxygen uptake (1)

Lactate concentration was determined in ar terilized capillary blood according to colorimetric method (2) immediately after submaximal and maximal work and 4 min. after maximal work

RESULTS AND DISCUSSION

Normal values were found as regards total lung capacity and vital capacity The forced expiratory volume during the first second, expressed as a percentage of the vital capacity is a measure of the degree of obstructive disease. Low values were found for group III, with 5 out of 10 boys below two standard deviations (Fig. 1) It is noteworthy that 2 of 3 boys in group I had asthmalike attacks during work and that 3 boys out of 10 in group III could perform maximal work without clinical signs of asthma. Bloodgas analyses of arterialized capillary blood at rest have been made and indicate that there is a slight alveolar hyperventilation especially among children with more advanced asthma as reflected in low values for CO_2-tension. The arterial oxygen tension in relation to the FEV % shows a correlation between the degree of obstruc tion as expressed by the FEV % and the arterial oxygen tension as evaluated from arterialized capillary blood.

Heart volume was in all cases within normal limits in relation to total amount of hemoglobin (5) The work intensity performed at a pulse rate of 170 was also within normal limits in relation to heart volume in all cases (5) Also in cases with severe bronchial asthma, the functional capacity was normal n relation to heart volume. Thus, there was normal relationship between function and dimension of the oxygen transport system at submaximal loads.

The maximal oxygen uptake has been related to the heart volume in prone position (Fig. 2) It appears that even children with severe asthma have a normal maximal oxygen uptake capacity There is no difference in the mean value of the maximal oxygen uptake for group I and II together as compared with group III.

In children with severe asthma the lactate con centration in arterialized blood was higher than in children with less pronounced bronchial asthma (Fig. 3) The underlying reason for the larger anaerobic component in children with severe asthma is unknown, but factors like arterial oxygen desaturation and increased work of breathing may be responsible

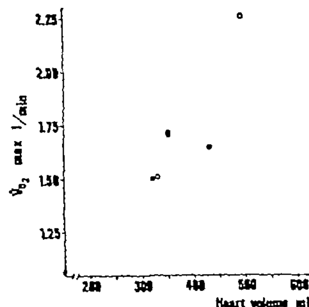


Fig 2.Heart olume in relation to maximal oxygen uptake (V_{O_2} max) in 20 boys with asthma.
x=mild asthma (group I)
o=moderately severe asthma (group II)
■=severe asthma (group III)
For detailed clinical classification see Table 1

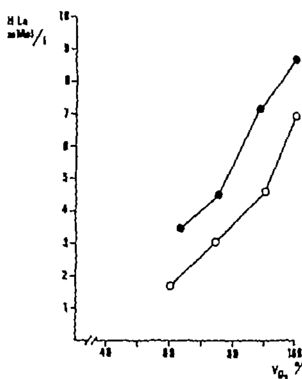


Fig 3. Lactate concentration in arterialized capillary blood (HLa) as fonction of the oxygen uptake during work expressed as percentage of maximal oxygen uptake (V_{O_2} %)
Symbols as in F g 2.

SUMMARY

1 The dimensions of the cardiovascular system as evaluated from heart volume, total amount of hemoglobin and bloodvolume were normal.

2. Even in the presence of marked obstructive changes, the oxygen transport capacity as evaluated from submaximal and maximal work loads, is normal. In this material no relationship between the degree of obstructive changes and the functional capacity has ben established.

3 Children with more severe asthma seem to work with a larger anaerobic component at maximal load than children with a less pronounced asthma.

4. Heavy work on a bicycle ergometer produced asthmatic symptoms in 50 % of the cases irrespective of the clinical severity of the asthma. The respiratory symptoms were not clinically typical for bronchial asthma and disappeared without treatment in less than 15 minutes.

ACKNOWLEDGEMENT

Supported by grants from the Wenner-Grenska Samfundet and the Smedby Foundation, Stockholm.

REFERENCES

1 Åstrand, P.-O *Experimental studies of physical working capacity in relation to sex and age.* Munksgaard, Copenhagen 1952.
2 Barker S B and Summerson, W H. The colorimetric determination lactic acid in biological material. *J Biol Chem* 138 535 1941.
3 Broman, B Dahlberg, G and Lichtenstein, A. Height and weight during growth. *Acta Paediat* 30: 1 1942
4 Crompton, G K. An unusual example of exercise induced asthma *Thorax*, 23 165 1968.
5 Holmgren, A Jonsson, B Levander M., Linderholm, H Sjostrand, T and Ström, G. Low physical working capacity in suspected heart cases due to inadequate adjustment of peripheral blood flow (aregulatory asthenia) *Acta Med Scand* 158 413, 1957

6. Hyde, J. S. and Swarts, C. L. Effect of an exercise program on the perenially asthmatic child. *Amer J Dis Child* 116. 383 1968.

7. Jones, E. S., Buston, M. H. and Wharton, M. J. The effect of exercise on ventilatory function in the child with asthma. *Brit J Dis Chest* 56 78, 1962.

8. Kjellberg, S. R. Rudhe, U and Sjostrand, T. The relation of the cardiac volume to the weight and surface area of the body, the blood volume and the physical capacity for work. *Acta Radiol* 31 113, 1949

9. Kraepelien, S., Engstrom, I. and Karlberg, P. Respiratory studies in children. Lung volumes in symptom-free asthmatic children. 6—14 years of age. *Acta Paed Scand* 47 399 1958.

10. McElhenney T. R. and Petersen, K. H. Physical fitness for asthmatic boys. A co-operative pilot study *Am Med As* 168. 178, 1963

11. Milman, M., Grundon, W. G. Kasch, F. Wilkerson, B. and Headley J. Controlled exercise in asthmatic children. *Ann Allergy* 23. 220, 1965

12. Petersen, K. H. and McElhenney T. R. Effects of physical fitness program upon asthmatic boys. *Pediatrics*, 35 295 1965

13. Rebuck, A. S. and Read, J. Exercise induced asthm *Lancet* 429 1968.

14. Scherr, M. S. and Frankel, L. Physical conditionin program for asthmatic children. *Am Med Ass*, 16 1996, 1958.

15. Sjöstrand, T. A method for determination of tot hemoglobin content of the body *Acta Physiol Scan* 16. 201 1948.

16. Vavra, J. Macek, M. and Spicak, V. La capacité d tra ail chez les enfants asthmatiques. *Re Pédiat* 3, 1969

Key words. Asthma, exercise tolerance, maximal oxyge uptake, blood lactate, spirometry heart volume, tot hemoglobin, blood volume.

(S.B.) Department of Clinical Physiology Södersjukhuse
100 64 Stockholm
Sweden

Acta Paediat Scand Suppl 217 1971

INTENSIVE PHYSICAL TRAINING IN CHILDREN WITH BRONCHIAL ASTHMA

J VAVRA, M. MACEK, B MRZENA and V SPICAK

From the Laboratory for research of physical fitness
Faculty of Pediatrics, Charles University Praha, Czechoslovakia

Exercise programs are nowadays included in the management of patients with bronchial asthma. These programs fall into two types

1 Breathing exercises directed towards the training of specific respiratory muscles and the prevention of thoracic deformities

2 General conditioning with the aim of improving physical fitness.

Both constituents are important for growing organisms in particular. Leaving the question of methods and results of specific breathing exercises aside, let us consider the problems of overall fitness exercises in asthmatic children. The general conditioning is designed to maintain or to regain both neuromuscular and cardiovascular efficiency. The specific physical conditioning programs for young asthmatics were devised and studied by various authors on groups of children in summer camps and in gymnasiums, and different sports activities such as gymnastics and swimming were practised.

MATERIAL AND METHODS

Our experience was obtained on a group of asthmatic children subjected to three months intensive physical training in gymnasium. The group consisted of 9 boys and 7 girls of 12 to 14 years of age, who were outpatients at a long follow up in Allergological dispensary. Their asthmatic complaints were classified as moderate. All of them were symptom free at the beginning of the exercise program. A great deal of them participated neither in the normal school physical education nor in other sports activities on account of illness, and the proposed exercise program was readily accepted by them as well as by their parents. The training was done three times a week for an hour and included gymnastic activities and ball games gradually increasing intensity. The training was supervised by the physical education teacher with the assistance of physiotherapeutists and a supervisory medical practitioner all of whom participed in a detailed individual documentation.

Before and after the three months training the rutine spirometry and the W_{170} index were examined as well as the maximum oxygen uptake and the arterial P_{O_2} and P_{CO_2} and pH during the maximum load on the bicycle ergometer

RESULTS

The results are shown in Table 1. The maximum oxygen uptake before training is in both boys and girls somewhat lower when compared with the results obtained in healthy Prague children of the same age. No increase could be found after the training program either in boys or in girls. The slight decrease is not statistically significant. Thus, we can conclude that the exercise program did not bring about any improvement of the aerobic capacity. More interesting results can be seen in the

Table 1 Values before and after training of asthmatic children

	$\dot{V}_{O_2}$ max ml/min/kg	W_{170} Watts/kg	P_{aO_2} mmHg	P_{aCO_2} mmHg	pH_a
Boys					
B 9	42	2.40	81	33	7.29
A 9	38	2.19	90	32	7.27
Girls					
B 7	35	1.80	77	33	7.34
A 6	35	1.76	86	32	7.36

blood oxygen pressure at the maximum work load. A certain increase can be proved in these values in both boys and girls at the end of the training period. This increase is just at the 5 % significance level. It could be regarded as an evidence of a better gas exchange in the lungs.

Of 16 children included in the group only 15 completed the whole training program. One of the girls withdrew because of deterioration of her complaints, but this was not due to the program. During the whole training period a slight degree of dyspnoe made suspension of exercise neccessary for two children only and even they were able to resume the program without any further complaints. In the first half of the training term, the exercise brought about a mild tiredness after training, which was however well tolerated by children and did not affect their desire for further training, and ceased in the second half of the whole period in spite of the progressive intensity of the exercise.

DISCUSSION

The three month period is too short to justify any conclusions about the benefits of physical training on the underlying disease process of bronchial asthma itself and this cannot be expected judging by the experience of others. Nevertheless, it can be concluded that our asthmatics accepted and tolerated the intensive physical training very well without any detrimental effect on the underlying disease. It did not improve their cardiovascular fitness judging by the oxygen transport capacity or by the heart rate exercise response. Several authors could prove the increase in cardiovascular fitness resulting from their exercise program in young asthmatics, some others did not find any. There is general agreement on the good tolerance of exercise programs in asthmatics and psychological benefits of it. A point we may recall the results of an interesting study by Chai and others from Denver who followed up 3 groups of young asthmatics of similar severity of the disease for a ten-month period. In addition to the general treatment, one group was treated by breathing exercises, the other group by conditioning exercises, and the third group was kept without any exercise. All three groups were examined repeatedly with very frequent medical contact that was equal in all groups. After ten months all groups showed similar improvement, consisting in a decrease in drug consumption, clinical improvement, and better functional indices. The main benefits were attributed to the frequent medical contact with its psychological influence on both children and parents.

On the other hand, owing to their lability of the bronchial tree, asthmatics are predisposed to the postexercise bronchospasms, which is not desirable, not only because of dyspnoe, but also for its unfavourable consequences to the deterioration of the ventilation-perfusion ratio in the lung areas and the pulmonary hemodynamics. In general, the post exercise bronchospasms in asthmatics supervene after 5 to ten minutes of sustained strenuous exercise. This risk calls on the one hand for the examination of the individual asthmatic as to the bronchial reaction to the exercise load, and on the other for the proper arrangement of exercises. Short intermittent periods of exercises, even of strenuous nature, are well tolerated without any undesirable reaction of the bronchial tree, and therefore preferable to the endurance training. Even this circumstance implies that the exercise suitable for asthmatics is directed most likely to the training of motoric skill, of neuromuscular coordination, and eventually of greater muscular strength, not being the training that could be expected to increase the cardiovascular efficiency evidenced by higher oxygen transport capacity and other indices.

The physical conditioning program seems un

likely to have any long term beneficial effect on the underlying asthmatic disease. In this connection, there is an interesting finding of improved blood oxygen pressure at the maximum exercise when comparing these values before and after the training period. This would suggest an improvement in gas exchange in the lungs, which is impaired in a great deal of asthmatics due to the inequality in ventilation perfusion. The authors are aware that this finding was made in a small group only and is by no means susceptible to generalization. We could not find any data of this kind in similar studies. Therefore we consider it to be an incentive to a further and more detailed study in this field.

Acta Paediat Scand Suppl 217 1971

WORKING CAPACITY AND PHYSICAL TRAINING IN ASTHMATIC CHILDREN, AT 1800 M. ALTITUDE

F. GEUBELLE, C. ERNOULD and M. JOVANOVIC

From the Pediatric Clinic, University of Liège, Belgium

For asthmatic children, living in the mountains is often considered as a so called climatic therapy. Moreover physical training is also used as a part of the treatment. Our study was performed in order to investigate the effects of these combined situations—altitude (1800 m) and physical training—on the working capacity of asthmatic children.

CLINICAL MATERIAL

Details on the physical and biological characteristics of the patients will be published (4); a short description is summarized in the following way.

Eleven asthmatic children, 5 girls and 6 boys, 7 to 14 years of age, have been observed before, during and after physical training in altitude.

The duration of the disease was between 3 and 10 years. 15 to more than 100 crisis or asthmatic attacks have been observed by the parents since the beginning of the disease.

One patient was considered as *mild* asthma (less than 5 crisis/year), eight as *moderate* (5 to 10 crisis/year) and two as *severe* (more than 10 crisis/year).

From clinical and laboratory findings, the etiological factors are appreciated and classified under the terms allergic and infectious factors.

The allergic factor is considered as prevailing when typical allergic syndroms (eczema, asthma, urticaria ...) are quoted in the family, typical change of the nasal mucosa are observed, skin tests are positive for one or more allergens which could provoke a bronchospasm, during a respiratory challenge.

The infectious factor is considered as prevailing if repeated bronchitis are observed, with mucopurulent sputum, blood-leucocytosis and pathologic shadows on the lung X-ray. Moreover bronchiectasis have been observed on the bronchography pictures in three patients.

The dominance is appreciated from a scoring, all the described items—allergic as well as infectious—being included.

Allergic factors were dominant in six patients and infectious factors, in two children.

Both allergic and infectious factors were equally involved in three patients.

The respiratory function was investigated at the sea-level, in a symptom free period.

a) Lung volumes are abnormal in most cases and from the simultaneous increases of the FRC (functional residual capacity) of the ratios FRC/TLC (TLC: total lung capacity) and RV/TLC (RV: residual volume) the lung is considered as largely over inflated in one patient, moderately inflated in 3 patients. The over inflation was doubtful or mild in 3 cases and the lung volume is normal in 4 patients.

b) The vital capacity was within the normal values, predicted from standing height (—12 % to +36 % of the mean)

c) The lung compliance was higher than normal in 4 patients as demonstrated by the high value of the ratio compliance/FRC. In one patient with bronchiectasis and a suspected lung fibrosis, the lung compliance is low

d) The total pulmonary flow resistance was higher than normal in 5 cases—the difference being significant when the figures are more than 150 % of the predicted value.
The bronchial obstruction was partly alleviated in 4 (over 5) cases by inhalation of a sympathico-mimetic drug: the flow resistance decrease was 25 % or more.
The methods and the predicted values, from studies in healthy children, have been published previously (5 6)

e) The hyper reactivity of the bronchial tree to aspecific irritant (i.e. histamine) was considered as severe in 6 patients whose bronchi responded to very small doses (20 to 100 smaller than by healthy children) The hyper reactivity was moderate in 4 cases and mild in one patient.

These figures demonstrate that a group of asthmatic patients may be un homogenous from point of view even if they are clinically similar and symptom-free.

In all but two cases (GLA, VAN) their physical activity at home was fully restrained since the beginning of the disease—i.e. 3 to 10 years.

During a period of three months, at 1800 m altitude, they were submitted to a hard physical training. Since the second week they were performing a mean of four hours per day of intensive physical activity footing in the mountains (up to five hours on a day) whatever the weather was, swimming, boxing and other physical exercises.

METHODS

Within a month befor and after the stay in altitude, the "working capacity 170 (WC 170) was measured by submaximal work on the bicycle Before during and after the stay a submaximal step-test was used

A. On the bicycle the method described by ADAMS and coll. was used (1) The heart rate is counted on the ECG record. The workloads are chosen in order to obtain an heart rate between 150 and 170 at the eighteenth minute this adjustment was successfully performed in most cases. The O_2 consumption and CO_2 production are measured by the Diaferometric open technic: the accuracy of the method is 5 % The ventilation is measured by a flow-meter the signal of which is integrated in order to obtain the tidal volume. By electronic summation, the ventilated volume per minute is recorded the accuracy of the method is 3 %

The mechanic of breathing—i e. the dynamic lung compliance and the pulmonary flow resistance —was continuously recorded. The intra-thoracic pressure changes were measured through an intra oesophageal catheter The accuracy of the method was previously investigated (6)

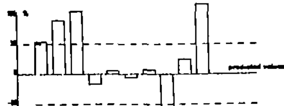
The reproducibility of the WC 170 values was estimated from duplicate determinations at few days or weeks—interval, in symptom free asthmatic children the differences are within 4 to 10 %

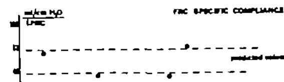
B For this preliminary investigation, bicycle and gas exchanges measurements in altitude were not available. The working capacity was thus appreciated by a submaximal step-test with a control of the heart rate on the ECG record.

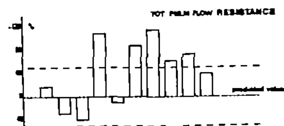
Three successive benches, are climbed during 3 minutes. The height of the benches are 16, 32 and 48 % of the distance between the pubis of the child and the ground.

The workload is calculated from the height of the bench, the weight of the child and the frequency of the climbing This frequency is choiced in order to adjust the workloads to similar figures used with the bicycle, assuming, at a first approach, that 80 % of the total work is used for the climbing and 20 % for the down movement. By plotting the heart rate versus the calculated workloads, the working capacity 170 was estimated.

The submaximal step-test was performed once within the month before the stay in altitude, twice







F g 1 Lung compliance, specific lung compliance of the functional residual capacity (FRC) and total pulmonary flow resistance in ten asthmatic children, at the sea level, before physical training at 1600 m altitude

during the first week and twice during the last week of the stay once again after the stay—i.e. at sea level.

From duplicate measurements at sea-level and at 1800 m. altitude (the last week of the stay) it can be concluded that the mean day-to-day variations is 6 % (range 1 and 15 %) in symptom free asthmatic patients.

RESULTS

1 The physical training period in altitude was considered as a "blind test period without continuous medical supervision except during the first and the last week of the stay

According to the record of the coach, the asthmatic attacks were less frequent and less severe.

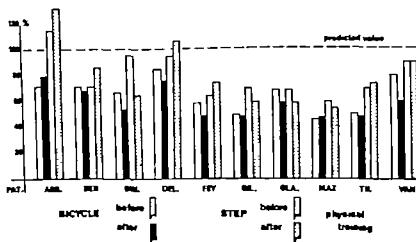
Except occasional administration of antihistaminic drug, all others therapeutic measures have been discarded (hypo-sensitization, sympathicomimetic drugs)

2 The results observed with the bicycle test are plotted on the predictive diagrams of ADAMS *et al* (1)

The W C. 170 of the 10 patients are lower than normal—*i.e.* the 50th percentile—in both instance before and after the stay in altitude (F g 2)

In healthy sedentary children and adolescents of our country the WC 170 is also lower than n the Californian boys and girls, observed by ADAMS *et al* But most of the values are between 80 and 100 % of the 50th percentile figures.

In asthmatic patients, the values are often



F g 2. WC 170 measured on bicycle and during submaximal step-test, before and after physical training at 1800 m altitude.

b) The vital capacity was within the normal values, predicted from standing height (—12 % to +36 % of the mean)

c) The lung compliance was higher than normal in 4 patients as demonstrated by the high value of the ratio compliance/FRC. In one patient with bronchiectasis and a suspected lung fibrosis, the lung compliance is low

d) The total pulmonary flow resistance was higher than normal in 5 cases—the difference being significant when the figures are more than 150 % of the predicted value.

The bronchial obstruction was partly alleviated in 4 (over 5) cases by inhalation of a sympathico-mimetic drug the flow resistance decrease was 25 % or more.

The methods and the predicted values, from studies in healthy children have been published previously (5 6)

e) The hyper reactivity of the bronchial tree to aspecific irritant (i.e. histamine) was considered as severe in 6 patients whose bronchi responded to very small doses (20 to 100 smaller than by healthy children) The hyper-reactivity was moderate in 4 cases and mild in one patient.

These figures demonstrate that a group of asthmatic patients may be un homogenous from functional point of view even if they are clinically similar and symptom-free.

In all but two cases (GLA, VAN) their physical activity at home was fully restrained since the beginning of the disease—i.e. 3 to 10 years.

During a period of three months, at 1800 m altitude, they were submitted to a hard physical training Since the second week they were performing a mean of four hours per day of intensive physical activity footing in the mountains (up to five hours on a day) whatever the weather was, swimming, boxing and other physical exercises.

METHODS

Within a month before and after the stay in altitude, the working capacity 170 (WC 170) was measured by submaximal work on the bicycle Before, during and after the stay a submaximal step-test was used.

A. On the bicycle the method described by ADAMS and coll. was used (1) The heart rate is counted on the ECG record. The workloads are chosen in order to obtain an heart rate between 150 and 170 at the eighteenth minute this adjustment was successfully performed in most cases. The O_2 consumption and CO_2 production are measured by the Diaferometric open technic the accuracy of the method is 5 % The ventilation is measured by a flow-meter the signal of which is integrated in order to obtain the tidal volume. By electronic summation, the ventilated volume per minute is recorded the accuracy of the method is 3 %

The mechanic of breathing—i.e. the dynamic lung compliance and the pulmonary flow resistance—was continuously recorded. The intra-thoracic pressure changes were measured through an intra-oesophageal catheter The accuracy of the method was previously investigated (6)

The reproducibility of the WC 170 values was estimated from duplicate determinations at few days or weeks—interval, in symptom-free asthmatic children the differences are within 4 to 10 %

B For this preliminary investigation, bicycle and gas exchanges measurements in altitude were not available. The working capacity was thus appreciated by a submaximal step-test with a control of the heart rate on the ECG record.

Three successive benches, are climbed during 3 minutes. The height of the benches are 16, 32 and 48 % of the distance between the pubis of the child and the ground.

The workload is calculated from the height of the bench, the weight of the child and the frequency of the climbing. This frequency is choiced in order to adjust the workloads to similar figures used with the bicycle, assuming, at a first approach, that 80 % of the total work is used for the climbing and 20 % for the down movement. By plotting the heart rate "versus the calculated workloads, the working capacity 170 was estimated

The submaximal step-test was performed once within the month before the stay in altitude, twice

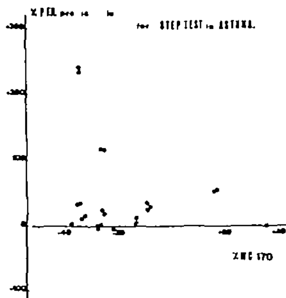


Fig 4 Relationship between the total pulmonary flow resistance (P.F.R.) and the WC 170 See F g 3.

the basal predicted heart rate on the other side the correlation is statistically significant. The lower is the heart rate in the sitting position—compared to the basal (7) but not to so called normal heart rate (8) in the sitting position —the higher is the working capacity

But no relationship is observed between the step-test working capacity on one side, the difference between the heart rate in the standing position and the basal predicted heart rate on the other side, except during the first week of the stay in altitude.

During the so called "period of adaptation from the sea level to the altitude, the higher is the heart rate in the standing position, the lower is the working capacity appreciated by the step test. A relative tachycardia—10 beats per minute *more than the heart rate at the sea level*—was observed only in 5 patients. In this group of asthmatic children, t seems that the heart rate in the standing position is indicating the working capacity and the cardiovascular fitness of the patient during the first days in altitude.

4. From 77 ECG records, abnormalities are classified in Table 2 as tachycardia, right axis deviation and—or—notching of the P wave, change of the QRS axis, flattening of the T wave in II and AVF depressed S-T segment 1—2 mm) abnormality of the right ventricular conduction and minor arrhythmias. In six patients, abnormalities have been observed before as well as after the stay in altitude in one child abnormalities disappear and in the last one, appear after the so-called climatic therapy The significance of the described abnormalities can not be appreciated. Indeed, as far as we know large study of the ECG standard deviations in healthy or asthmatic children, has not been performed and compared, before and during physical exercise.

However it is pointed out that strictly normal ECG records were observed in 20

Table 1. ECG abnormalities ... asthmatic children before (B) and after (A) three month physical training at 1800 m altitude

	Normal		Tachycardia		P-axis or abnormal P waves		QRS axis		T wave flattening (II, AVF)		Depressed ST segment (1—2 m)		Abnormal R.V conduction		Minor arrhythmia	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
Lying	3	6			2	2						1	2	3	1	1
Sitting	3	2		1	1	7		1	2			1	2	2		
During effort	6	2			2	6				3		1	2	2		
After effort (sitting)	4	2		3	2	6				2	3	2	2	2		1

(15 experiments over 20) less than 70 % of the normal predicted value. Low values have also been observed in a larger group of asthmatic patients whose level of physical activity was low

In most cases (7 over 10) there was a slight decrease—from 3 to 20 % of the predicted value—of the WC 170 after the stay in altitude. The working capacity 170 was not better after three months of intensive physical training.

3 Relatively small (±10 %) and erratic changes of the working capacity measured by the step-test, are observed *in seven patients during* the stay in altitude. In four patients, these changes are larger (up to 30 %) but still they are erratic.

The values of the step-test WC 170 before and after the stay in altitude are similar (±15 %) in seven patients. The working capacity is higher (+21 %) in one child (ASS) and lower (—29 %) in one patient, after the stay in altitude (BRI)

In all but one case, the working capacity 170 of these asthmatic patients, as estimated by the step-test, is not better after the three months physical training in altitude.

DISCUSSION

1 Discrepancy between the bicycle test and the step-test data will not be discussed here shortly it can be stressed out that differences less than 15 % are not significant owing to respective day to day variations of the WC 170 values from the bicycle and the step-test. Moreover further study of the gas exchange demonstrates *that the gas exchanges are not similar in* both tests, the oxygen pulse being higher when the child is working on the benches. Finally step and bicycle tests are performed at 24 hours interval in symptom-free patients. But the respiratory and the cardio-vascular function might not be identical from one day to the other in some patients.

2. From ventilatory point of view there is no relationship between the decrease of the WC

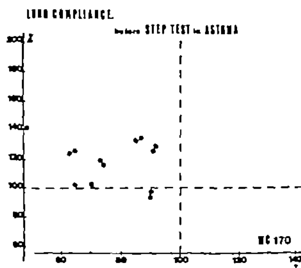


Fig 3 Relationship between the lung compliance, in % of the predicted value, and the WC 170 measured during a submaximal step-test, before, during and after physical training at altitude.

170 on one side, and the abnormal values—if any—of the vital capacity the functional residual capacity and the total lung capacity on the other side

The lung of some patients is over inflated but their WC 170 is relatively high in some others it is relatively low

But in most cases when the over inflation of the lung appeared or was more pronounced after the stay in altitude, the WC is decreased.

It seems that—from working capacity point of view—the patient is adapted to a degree of over inflation. If the lung will be more inflated, the WC 170 will be lower

The mechanic of breathing in symptom-free asthmatic children will not influence the WC 170. Indeed there is no relationship between the WC 170 on one side, the total pulmonary flow resistance and dynamic lung compliance on the other side (fig 3 and 4)

When the specific compliance of FRC is plotted against the working capacity no relationship is observed between these two parameters.

3 From cardiovascular point of view a relationship is observed between the bicycle working capacity on one side, the difference between the heart rate measured in the sitting position and

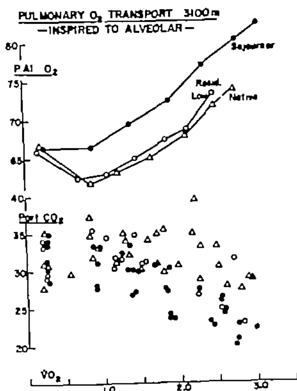


Fig. 2. Ventilatory responses to steady-state work in 3100 m hypoxia. Individual subject ($PaCO_2$) and group mean (calculated $\overline{P}A\ O_2$) values in sojourners, residing lowlanders and altitude natives. No systematic differences noted among groups at rest (each point = mean of 4 steady-state measures per subject).

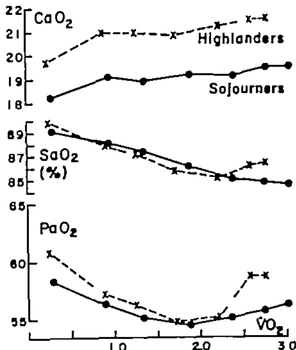


Fig. 3. Pulmonary O_2 transport at rest and during work at 3100m altitude. Arterial oxygen content (CaO_2) ml/100 ml, arterial oxygen saturation (SaO_2) and arterial oxygen tension (PaO_2) mm Hg mean values in sojourners and combined highlander groups.

contrasts among the varying periods of hypoxic exposure in the quality of pulmonary adaptation.

The resting ventilatory response to induced isocapnic hypoxia was, as expected, significantly reduced in altitude natives but was also depressed to a similar degree below sojourner values (~50%) in lowlander natives of long-term altitude residence (Fig. 1).

The ventilatory response data in Fig. 2 does not permit isolation of group differences in sensitivity to specific ventilatory stimuli, but does provide direct application to the question of inspired to alveolar gas transport under conditions approximating daily life at 3100 m. As with the resting hypoxic response studies (a) the groups were not differentiated until an extra stress (i.e., exercise in this case) was added over that existing under resting ambient conditions and (b) significant group differences with work were noted only in the ventilation and CO_2 retention in the native and residing lowlander relative to the sojourner with no differences in response among subjects of >2 years altitude residence. The altitude residents greater degree of CO_2 retention ensured their maintenance of a depressed alveolar PO_2 with work.

Figure 3 shows that altitude residents avoided this potential arterial desaturation via their maintenance of relatively narrow alveolar-arterial PO_2 exchange gradient over all work intensities. Even in heavy work where all subjects over ventilated the sojourner merely furthered his degree of arterial hypoxemia, whereas the highlander maintained A-a DO_2, and arterial and alveolar PO_2 rose concomitantly. The elevated arterial O_2 con-

Table 1 Physi al character stics—mean ±SE (ang)

Time at 3100m	Age yrs	Height cm	Weight kg	TLC L, BTPS	mlO₂/kg	Maximal Work heart rate	Base Excess meq/l
Sojourning Lo Lander (=10)							
45 days	27.8±1.8 (21-40)	178±3 (174-183)	71 4±2 (58-83)	6 2± 16 (5 4-6 8)	42±1 3 (36-51)	178±2 (169-191)	13.7± 3 (1 .0 to 16 0)
Alt Residing Lo landers (n=10)							
8.6 (± 6) (2—16 yrs)	17 5±0.3 (16-19)	174±2 (163-188)	63.5±2 (53-73)	6.0±45 (4 8-7.2)	40±2.0 (35-44)	184±4 (174-198)	10.9±1 1 (-9 0 to 14 6)
Altitud Nat es (n=9)							
1—3 generations	19.0±1.3 (18-30)	177±2 (168-187)	69.2±2 (54-79)	6.1± 19 (5 1 7 1)	39±1 1 (34-44)	181±2 (172 197)	10 2±.8 (-8.0 to 16.1)

All 29 subjects were used for the resting hypoxic response tests. Resting pulmonary functions and exercise data was collected on all 10 sojourners, 8 altitude natives nd 5 residing lowlanders.

hypoxic ventilatory response tests which were in the supine position. The exercise test consisted of treadmill walking with continuous work period of 17—20 mi utes over 3 elevations up to 8 % grade followed by intermittent w rk (of 4—4.5 mins) and rest sessions with 5 % increments in grade for each subsequent work load to level of maximum volitional effort. See Tab 1 This criterion was established i all sojourners and in 8 of 13 highlanders, but only 7 subjects in total achieved the more objecti criterion of a plateau or fall in VO_2 as eadmill grade was elevated in heavy work. Arterial lood was sampled anaerobically and analyzed polarographically D_LCO was measured at 2 or 3 alveolar oxygen tensions both by single-breath and steady-state techniques Qc was determined in the single-breath C_2H_2 ptake method in sojourners (2) and was presumed to have similar average relationship with VO_2 in highlanders (1) Expired gases were analyzed by both Sch lander and polarographic techniques for CO_2 and O_2 and by infra red analysis for CO and C_2H_2.

RESULTS

Pertinent findings are summarized in the order of their occurrence in the gas transport chain from inspired to tissue capillary PO_2 with emphasis on

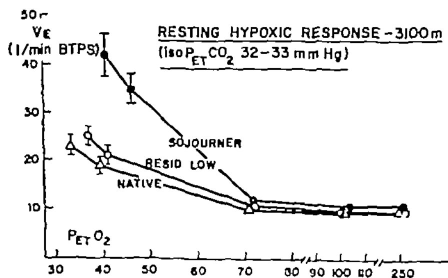


Fig 1 Resting steady state entilatory response to isocapnic hypoxia at 3100 m altitude in sojourners (45 days, n=10) lowlanders residing at 3100 m (2—15 yrs, n=10) and altitude na ti es (n=9) Mean alues ±SE

(18) found neglibible differences in their comparison of alveolar dimension and pulmonary surface volume relationships between sea level and altitude native guinea pigs and sheep. Similarly present findings suggest similar maximal diffusion surface areas in residents and sojourners based on their similarity in total lung volumes and the speculation that subjects of all groups were *approaching similar values for maximum* D_LCO and Vc at peak exercise. A temporary alternative explanation, based on functional differences between sojourners and residents in the size, distribution and expandability of the pulmonary vascular bed, is supported by reports of a large total circulating blood volume (53) and markedly *increased rest and work pulmonary arterial pressures* in Leadville natives of all ages. In addition, this postulate is consistent with our indirect evidence of more uniform $V_A.D_L:Q_0$ distribution in the exercising altitude resident and with the relatively marked expansion of pulmonary capillary blood volume from rest to light work. Perhaps the *proposed development of chemoinsensitivity* with accompanying exercise CO_2 retention in our maturing resident lowlanders precipitated the synergistic pulmonary vasoreactive effects of acid pH hypoxemic combinations, thereby effecting re distribution of $\dot{Q}_c$ to *previously over ventilated* areas (9).

The completeness or end-point of the pulmonary response to hypoxic work in terms of homeostasis of resting arterial oxygenation was comparable between sojourners and residents. The resident, by virtue of his enhanced O_2 carrying capacity presented *a higher exercise systemic* O_2 *delivery* but quantitatively the significance of resultant differences in $P\bar{v}O_2$ to duration or magnitude of aerobic energy expenditure in man is unclear (*10, 17 21 23*). The reported redistribution of blood flow (7) and *decreased* O_2 *Hgb affinity* (*12*) *at altitude* would potentially buffer the fall in working tissue PO_2 but the magnitude of such effects (+1—3 mmHg $P\bar{v}O_2$) are probably comparable in sojourners and residents. Similarly a 1 to 2 mmHg conservation of critical tissue PO_2 may be realized with altitude residence via increases in either tissue capillarization and/or affinity of the terminal oxidose system, but such adaptations were not apparent in acclimatized animals below 4100 m altitude (17).

It is proposed, then, that the critical difference between sojourners and long-term residents at 3100 m resides in the relative efficiency of their pulmonary adaptation. All subjects during even moderate *exercise at altitude are confronted with highly* potent, synergistic respiratory center stimuli in the form of hypoxia+work+altitude aclimation (3 4). The sojourner utilizes the full potential of such stimuli as manifested in his high respiratory rate, over ventilation, CO_2 release and maintenance of a high level of alveolar oxygenation and alveolar *mean capillary diffusion gradient throughout work*. The critical importance of such an adaptive mechanism is realized by estimating that its removal alone would have precipitated reductions up to 20 % in O_2 delivery and 5 to 18 mmHg in enous PO_2 with work at 3100 m. However the physiologic cost of this adaptation was high. In seven sojourners we measured a *significant increase* over sea-level values in flow-resistance ventilatory work during exercise at altitude (19) Furthermore, in all sojourners we observed a marked "awareness of one's hyperventilation during a variety of exercises, which was eliminated upon inspiration of high oxygen mixtures. To the contrary altitude natives and resident lowlanders, regardless of their relative maximum performance capability were resistant to the potentially potent interactive ventilatory stimuli presented to them and thus voided the high respiratory rates and accompanying exertional dyspnea. *In effect then, the resident's superior diffusing* capacity and more uniform pulmonary blood gas distribution "permitted his relative CO_2 retention and narrowed *alveolar-capillary diffusion* gradient without compromising the relative adequacy of his systemic O_2 transport. It is yet to be determined if the cost of enhancing pulmonary perfusion via increased vascular pressure and resistance exceeds in the long-term the proposed benefits to be derived from preserving a balance between ventilatory demand and effort.

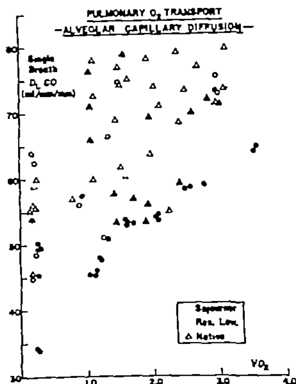


Fig 4 Individual subject values for single-breath diffusing capacity (D_LCO) at rest and during work (P_IO_2= 100, P_AO_2=44-88 mm Hg) Sojourners had significantly lower values than altitude residents but no differences were evident between altitude residing lowlanders and altitude natives.

tent in the highlander approximated values achieved in normoxic work at 250 m, secondary to their higher hemoglobin content.

The key to the highlander's low alveolar to arterial transport gradient is represented in Fig 4 by their superior rest and exercise alveolar-capillary diffusion. Further analysis showed a higher pulmonary capillary blood volume (Vc) in the altitude resident at all workloads. Approximately 80 % of the total exercise effect on Vc was completed by one l/min VO_2 in the resident, in contrast to the more linear VO_2-Vc relationship in the sojourner

DISCUSSION

Results of the present study elicit three questions requiring brief interpretation

1 Why are the resident lowlanders unique in their approximation of the ventilatory hyposensitivity to severe hypoxia and hypoxic exercise characteristic of the altitude native?

2 What adaptive mechanisms are responsible for the highlander's superior quality of alveolar-capillary-arterial gas exchange?

3 Do the described pulmonary adaptions contribute significantly to the quality of life and indeed long term "survival" itself at 3100 m?

It is proposed that the apparent chemoinsensitivity displayed by the resident lowlanders in adolescence was acquired with exposure to altitude during a period of maturation (3 mos—16 yrs) when peripheral chemoreceptor sensitivity was still amenable to environmental modification. Reported findings to date are equivocal in support of this hypothesis. The hypoxic ventilatory insensitivity observed at sea level in cyanatic congenital heart disease (5 16) is consistent with our implication that genetic factors need not be invoked as an explanation for the blunted ventilatory responsiveness in altitude residents. Furthermore, studies of ventilatory response to acute hypoxia in the human neonate have demonstrated a depressed or poorly maintained hyperventilation which matured up to 12—84 days after birth (14) On the other hand, later studies have shown that the hypoxic response in the newborn lamb and rabbit is adult like and dependent upon the integrity of the carotid chemoreceptors and that the carotid body is histologically mature early in gestation. A change in sympathetic innervation or local vascular supply might be capable of modifying carotid body sensitivity throughout the growth period, as it apparently does upon transition from foetal to neonatal life.

An explanation for the increased diffusion capacity and narrowed alveolar-arterial O_2 transport gradient in the highlanders may be based on morphologic and/or functional differences, both of which may be critically influenced by age of initial hypoxic exposure. Structural adaptation with long-term altitude residence appears as a logical explanation based on reports of the continuous, dynamic growth through adolescence of alveolar diameter and number and of the dimensions of the pulmonary vascular bed (6, 21) It must be presumed then, that the pulmonary effects on environmental oxygen lack potentiate those of increasing endogenous metabolic need commensurate with growth. To the contrary Tenney and Remmers

Act P ediat S and S ppl 17 1971

EFFECT OF PHYSICAL TRAINING ON CENTRAL AND PERIPHERAL CIRCULATION IN ADOLESCENTS WITH MOTOR HANDICAPS

AKE LUNDBERG

From the Med al M di al Depar m nt Norrbackainstitutet Stockholm S de

Lundberg, Ovenfors and Saltin (6) and Ekblom and Lundberg (2) showed that students w th motor disturbances due to cerebral palsy my elomeningocele and other causes of motor handi caps significantly increased their exercise tolerance in connection with physical training The cal culated maximal oxygen uptake capacity was simi larly increased, while the heart rate and blood lac tate during exercise were lower than before the period of training

These observations are in agreement with other reports on the effect of physical training in normal men (3 4) as well as in groups of patients with various diseases, such as coronary heart disease (8) vasoregulatory asthenia (5) and mental disorders (1) From these reports it is ev dent that physical training provokes an increase in the ventilatory and circulatory dimensions and thereby the oxygen transport capacity

Lundberg and Pernow (7) studied submaximal work on a bicycle ergometer before and after 6 weeks of physical training by adolescents with cerebral palsy or post traumatic hemiplegia. Exer cise performance increased on an average 18 per cent. At a given submaximal work load, heart rate was significantly lower after the training, whil pulmonary ventilation and oxygen uptake were un-affected. Arterio-venous oxygen difference and venous-arterial lactate difference over the exer cising leg was significantly lower after training. No significant change was observed in the arterial inflow capacity of the leg

The evidence of the increased exercise tolerance in connection with the training serves to indicat the benefit of physical training in rehabilitation of motorically handicapped adolescents.

REFERENCES

1 Carlsson, C Dencker S. J Grimby G & Häggendal, J Circulatory studies during physical exer cise in mentally disordered patients. II. Effects of physical training in patients w th and without administration of chlorpromazine. *Acta med Scand 184* 511, 1968.

2 Ekblom, B & Lundberg, A Effect of physical training on adolescents with severe motor handicaps. *Acta Paediat Scand 57* 17 1968.

3 Ekblom, B Åstrand, P O Saltin, B Stenberg, J & Wallström, B M Effect of training on cir culatory response to exercise. *J Appl Physiol 24* 518, 1968.

4 Frick, M H Konttinen, A & Sarajas, H. S. S. Effects of physical training on circulation at rest and during exercise. *Amer J Cardiol, 12.* 142, 1963

5. Holmgren, A Jonsson, B., Levander M Linderholm, H Mossfeldt, F Sjöstrand, T & Ström, G. Physical training of patients w th vasoregulatory asthenia. *Acta Med Scand 158* 437 1957

6. Lundberg, A Ovenfors, C-O & Saltin, B. Effect of physical training on school-children with cerebral palsy *Acta Paediat Scand 56* 182, 1967

7 Lundberg, A & Pernow B The effect of Physical Training on Blood Flow Through Exercising Muscle in Adolescents w th Motor Handicaps. *S and J Clin Lab Invest, 26.* 89 1970.

8. Varnauskas, E Bergman, H Houk, P & Björntorp, P Haemodynamic effects of physical training in coronary patients *Lancet 2,* 8, 1966.

Key ords Physical training, cerebral palsy myelomeningocele.

REMARKS ON PHYSICAL TRAINING OF CHILDREN WITH CEREBRAL PALSY

KRISTINA BERG

From the Department of Pediatrics, University of Göteborg, Göteborg, Sweden

As an introduction, a film was shown, which demonstrated different methods used for training of children with severe affliction of cerebral palsy

As seen from the film, the material studied had severe handicaps. For this reason, it was not possible to apply conventional tests of physical working capacity to this material. On the opposite, several adaptations of the agreed procedures were necessary. Since the modifications of the test methods have been published recently (2) only a summary will be given here. Most children could not participate in air collections at their maximal work intensities. Then the oxygen uptake was determined at two or more submaximal heart rate levels. The determinations were connected with a straight line on a graph. The maximal heart rate was determined separately in each subject. The observed maximal oxygen uptake was obtained by extrapolation of the line to the observed maximal heart rate (Fig. 1 line A_1—A_3)

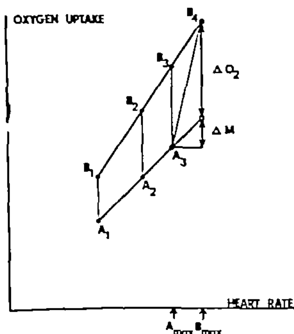


Fig. 1 The graphical procedure for reading the "observed maximal" oxygen uptake. For explanation see text

If training was efficient in raising the oxygen uptake capacity (Fig. 1 ΔO_2) a higher oxygen uptake was found at the different submaximal heart rate levels (Fig. 1 line B_1—B_3) Often, the maximal heart rate observed before training was below what could be expected for age. One frequent training effect was a rise of the observed maximal heart rate, which enabled the child to use circulatory capacities, which had been out of its rach before (Fig. 1 ΔM) presumably because of muscular weakness.

To motivate the labour and expenses, required for physical training of children with cerebral palsy I will now present some of the results observed in our studies (2)

Before training, the "observed maximal" oxygen uptake had a mean value of 57 % of normal values, given by Astrand (1) and calculated per

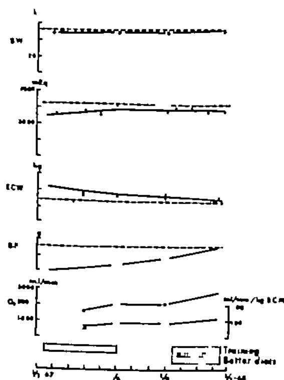


Fig 2. Effect of physical training alone and combined with improved nutrition on body composition and on observed maximal" oxygen uptake in one 18-year old boy with dyskinesia. BW—body weight, K,—total exchangeable body potassium, ECW—extra cellular water BF—body fat, BCM—body cell mass, and O_2— observed maximal" oxygen uptake. Solid lines connect the observed values, dashed lines the values predicted from height, age and sex.

kg body weight. Calculated for the cell mass, the mean value was 71 %. After physical training, 19 of the 21 subjects had increased their "observed maximal" oxygen uptake, and the increase was roughly proportional to the training period, up to about 12 months. Twelve of the 21 subjects increased their "observed maximal" oxygen uptake by more than 25 %. The final results of all subjects showed a mean value of 75 % of normal values, calculated per kg body weight, and of 90 % calculated per kg body mass.

The children themselves often expressed well being after training started. Many students appeared more active, and some were reported to need less rest periods in school. Such effects were not well correlated to actual increases in their physical capacity ($\dot{V}_{O_2 max}$), however.

The effects on the body composition of training was also studied. The body composition was determined with isotope dilution methods, using 42K and THO as tracers. Body cell mass (BCM), total body water (TBW), extracellular water (ECW) and body fat (BF) were then studied. Before training, the subjects demonstrated a reduced BCM for age and for height, and an abnormal increase of TBW and ECW. Training alone reduced the water (Fig. 2). The mechanism for this effect is not fully known. However, one factor contributing to this effect, was improved nutrition from better appetite. Training in combination with a more nutritious food reinforced the tendency (Fig. 2). Improved nutrition without training caused no significant effects on body composition in our material.

One issue to be discussed in our studies regards the appropriate reference point. The unit body weight (BW) is commonly used, since BW is easy to measure, and the unit is relevant if one is interested in the subject's ability to move around. In the cerebral palsy material it was evident that great changes occurred during training in the body composition, affecting also body weight. So an increase noted during training of oxygen uptake per kg BW could be due to a higher oxygen uptake capacity, a decrease in BW from loss of water, or both. So if one is interested in studying these effects separated from one another, BCM is preferable. Where whole body counting is available, it is also a simple procedure to determine BCM.

REFERENCES

1. Åstrand, P.-O. and Rodahl, K.: *Textbook of work physiology*. McGraw-Hill Book Company, New York, 1970, p. 511.

2. Berg, K.: Adaptation in cerebral palsy of body composition, nutrition and physical working capacity at school age. *Acta Paediat Scand*. Suppl 204, 1970.

Key words: Physical training, cerebral palsy, oxygen uptake, body composition.

MAXIMAL AEROBIC CAPACITY OF 6—15 YEAR-OLD GIRLS AND BOYS WITH SUBNORMAL INTELLIGENCE QUOTIENTS

O BAR-OR, J S. SKINNER, V BERGSTEINOVA, C. SHEARBURN, D BOYER, W BELL, J HAAS, and E. R. BUSKIRK

From the Laboratory for H man P formanc Res arch I stitute for S I nce and Eng neering, The Pen yl ania State Uni rsity Uni rsity Park Pa. U.S A.

Research on the relationship between children s intelligence and their ability to perform a physical task has shown a lower performance level in the mentally retarded than in the intellectually normal child This was shown in number of studies in which the test items included a variety of individual motor performance tests, as well as batteries of items to determine physical fitness

The reason for such subpar performance is not yet clear It is generally concluded that children with subnormal Intelligence Quotients (I Q) score especially badly in skill items which require learning and neuromuscular coordination (5 6, 11) Low scores could also be attributed to growth, development and sexual maturity which were slower in markedly retarded children (1 3, 7 9) Little is known, though, of the cardiorespiratory response to exercise in mentally retarded children, and whether this system is in any way related to their subnormal motor performance. Asmussen and Heeboll-Nielsen ( ) found lower maximal inspiratory and expiratory forces in 62 boys with I Q of 70—90 when compared to age-or height-matched boys with I Q s higher than 95 No comparative n formation is available on other pulmonary functions of these boys.

The purpose of this study was to determine the aerobic capacity of a group of children with I Q ranging between 50 and 90 This was done by the maximal oxygen consumption (V_{O_2} max) measurement, which is considered the best single measurement to determine an individual s capacity for strenuous muscular exercise lasting a few minutes or more.

MATERIALS

Data are presented on 72 girls and 89 boys who participated in an all-out treadmill walk which was part of a Growth, Development, and Performance study held at the Pennsylvania State University These represented a sample from a population of school children from Central Pennsylvania whose I Q s, as determined by group testing at their schools, were below 95 The Wechsler Intelligence Scale for Children (15) was given individually to each of the selected participants on the same day as the exercise tests such individual testing is considered more representative than group testing. I Q s from the Wechsler test, therefore, are referred to in this report.

The children underwent a medical examination performed by the school physicians. Excluded were those with neurological musculoskeletal, cardiac, and pulmonary disorders which might interfere with a successful exercise test Further elimination was caused by refusal on the part of some parents and by 5 med al exclusions by the research physi ian Th test group therefore is not a random

This esearch was partially supported by U S Off of Education Grant OEG-0-8-0-6-4-1-5 6-0

Table 1. I.Q., age and physical characteristics of mentally retarded girls and boys by age groups. Means and 1 S.D.

Age Group	I.Q.	Chronological Age yrs	Skeletal Age yrs	Dental Age yrs	Weight kg	Height cm	Body Density
			Girls				
6—7.9	85.6	7.1		3	23.–	1 1 1	1.033
n=9	3.0	0.5	1.(	0.7	3.3	4.8	0.014
8—9.9	70.5	9.4	10	9.0	28.5	130.9	1.027
n=6	9.7	0.7	0.4	0.9	6.4	7.7	0.014
10—11.9	71.6	11.2	11.1	11.1	34.5	143.9	1.029
n=10	7.3	0.5	1.3	0.8	6.4	9.5	0.003
12—15.5	73.8	13.5	13.2	13.2	43.9	152.0	1.04–
n=19	11.4	0.9	1.3	1.6	15.5	8.3	0.014
			Boys				
6—7.9	79.2	7.3	6.7	7.8	3 3	120.6	1.034
n=6	6.6	0.6	1.5	1.5	1.7	8.8	0.007
8—9.9	78.7	8.4	7.8	8.4	25.0	126.5	1.037
n=13	7.4	1.0	1.8	1.0	4.4	7.5	0.014
10—11.9	71.6	10.8	10.6	11.1	32.1	139.5	1.035
n=14	7.2	0.3	1.8	1.3	4.4	6.9	0.00
12—15.5	72.2	13.6	14.2	13.4	45.8	154.6	1.036
n=28	10.0	1.0	1	1.4	12.9	9.4	0.014

Calculated from skinfolds according to Pařízková

sample of the population. Most of the participants (n=146) lived at home and attended regular schools. The others (n=15) lived in a State Institution.

As found by the Wechsler test, 125 children had an I.Q. of less than 90. One hundred and five of these successfully completed the all-out walk and constituted the test group ("low I.Q." group). Their ages, I.Q. and physical characteristics are summarized by age-groups in Table 1. Thirty-six children had I.Q. of 90 or more. Those who completed the walk (n=32) were used as a control group. Their ages, I.Q. and physical characteristics are summarized in Table 4.

METHODS

Testing was performed during spring, 1969. None of the children had previous experience with treadmill walking or with other test procedures employed in this study. After 2—4 minutes of practice to determine that the child could walk comfortably he rested for 4 minutes, during which time the test procedure was explained. He then was given a 3-minute warm-up walk at 5.6 km/hr 7.5 % grade, while being connected to the gas collecting apparatus.

Children were sequentially assigned to 3 different walking protocols to determine their $\dot{V}_{O_2}$ max. Protocol A was a 2-min progressive continuous test, protocol B was a 3-min progressive continuous test, and protocol C, a 4-min progressive interrupted test. Walking speed for all protocols was 5.6 km/hr with slope increments of 2.5 % at the end of each work period. A detailed description and analysis of the three protocols is reported elsewhere (10). Since all three procedures yielded similar $\dot{V}_{O_2}$ max results, this report will combine all data, irrespective of the protocol used.

In addition to the treadmill walk, anthropometric, developmental, and muscle strength data were obtained. Reported here are the dental age, skeletal age, and skinfold thickness. Dental age was evaluated by the research physician from the number of erupted permanent teeth according to Tanner (

Table 2. *Causes of noncompletion of all-out test*

Refused to walk	5
Refused to complete walk	12
Refused mouthpiece	3
No coordination (or ataxia)	4
Total	24

Just erupted teeth and extracted permanent teeth were included in the count. Skeletal age was assessed by the Tanner Whitehouses method (13, 14) from postero-anterior radiographs of the right wrist and hand. A portable 15 ma x ray machine was used at a focal length of 100 cm, at 55 kv Skinfolds were measured by a Lange caliper from 9 sites cheek, chin, forearm, chest, subscapula, side, waist, abdomen and leg (poplites) Body density was evaluated from the sum of the skinfold thickness according to Parizková (8) The regression lines for 9—12 year-old children in her report were used for all children up to 12 years of age.

RESULTS

Thirteen girls and 11 boys could not complete the all-out test. These represented 15 % of the exercising group. Causes of noncompletion are summarized in Table 2. Although there was no predominance of a certain age group among these children, low I.Q may be a contributing factor to incompletion of the test as indicated in Table 3 More striking is the importance of place of residence while only 10 % of the children living at home did not complete the test, 60 % of the institutionalized children did not complete it.

The maximal values of HR, V_{O_2} (l/min) and V_{O_2} (ml/kg min) are plotted against age in Figure 1 The girls had a significantly ($p<0.05$) higher maximal HR as a group and also at the age

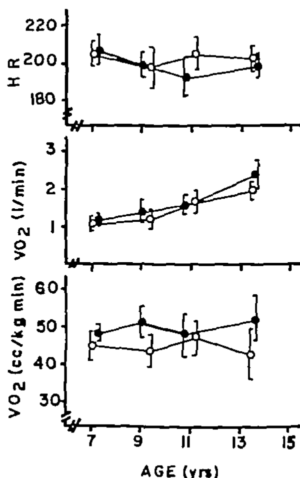


Fig 1 Maximal physiological changes for boys (●) and girls (0) in relation to chronological age.

group 10—11 9 years. Differences in maximal HR at other ages were not significant. V_{O_2} max, when calculated in absolute values, showed a continuous increase with age. It was higher in the boys at all ages, but significantly so ($p<0.01$) at the 12—15 5 age group only However when V_{O_2} max was calculated per kg body weight the boys had significantly higher values ($p<0.01$) at the 8—9.9 and 12—15 5 age groups.

Table 3 *Completion of exercise test in relation to I Q and to place of residence* Number of children and %

	IQ ≤79	IQ ≥80	Institution	Home
Total children	81 (100 %)	60 (100 %)	15 (100 %)	146 (100 %)
Exercised	63 (79 %)	4 (93 %)	6 (40 %)	131 (90 %)
Refused or unable to complete test	18 (1 %)	6 (7 %)	9 (60 %)	15 (10 %)

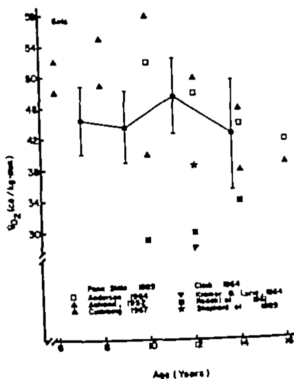


Fig. 2. Maximal oxygen consumption of mentally retarded girls with mean ±S.D. at different chronological ages. Comparison with data in the literature.

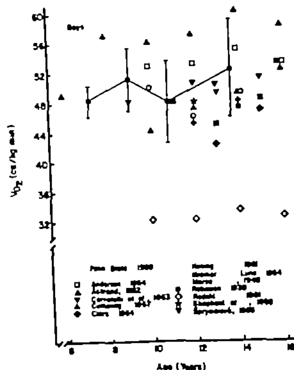


Fig. 3. Maximal oxygen consumption of mentally retarded boys with mean ±S.D. at different chronological ages. Comparison with data in the literature.

In Figures 2 and 3 a comparison is made between the $\dot{V}_{O_2}$ max of mentally retarded girls and boys, respectively and mean values obtained from the literature for children. The data from the present study fall well within the range reported in the literature. However, when the low-I.Q. children are compared to the control group (Table 4) the boys from the former have significantly lower $\dot{V}_{O_2}$ (ml/kg · min). The corresponding differences for the girls are not significant. All other physiological parameters for boys or girls were not significantly different, when comparing the low I.Q. children with the control group.

DISCUSSION

Both a child's intelligence and his rate of physical growth and development result from a complex interaction of genetic, environmental, psychological, and social factors. Whether a common factor can be identified which causes both mental retardation and subpar physical performance is of academic and practical importance, but our current state of knowledge does not offer a clear solution. This is mostly because "mental retardation" is not a single phenomenon and, therefore, it is impossible to find a common denominator, e.g., for a low I.Q. condition caused by an organic disease and for one resulting from a problematic social environment. For this reason, it would be surprising if one found a certain physiological response to exercise which is inherent to large groups of retarded children. The finding of significantly lower $\dot{V}_{O_2}$ max in the low I.Q. boys compared with the controls cannot be generalized, therefore, for other groups. Nor can one find a satisfactory explanation for this finding: as seen in Table 4, there were no significant differences in body height, weight, or density of the two I.Q. groups. This excludes the possibility that the differences in aerobic capacity are

Acta Paediat Scand Suppl 217 1971

PHYSICAL CAPACITIES OF MENTALLY RETARDED CHILDREN

FRED W. KASCH and S. A. ZASUETA

F m the S D g Stat Coleg San Dieg Califor a, U S A

The need for physical activity in the mental emotional, and physical development of the edu cable mentally retarded (EMR) child has been recognized by a number of workers (14 17) The old "taboo has lifted. Educators, physicians, and therapists have become more aware of the potential capacity of the EMR child. Yet the problem is great. In the United States alone there are approximately seven million retarded children with 120 000 being added annually This is a tremendous educational and humanitarian challenge

What can we expect from the EMR in the realm of physical accomplishment? What levels of achievement should we anticipate. Howe (8) found the EMR compared favorably with the normal youngster in grip strength, throwing accuracy and learning patterns Koegh (13) discovered that the EMR group scored at one-third to one half of the level of performance of normal boys in the motor skills. On one skill, namely hopping, the normals were surpassed by the EMR group

Hart (7) and Ismail (9) found that a relationship exists between physical ability and academic achievement. Geddes (6) concluded that crawling patterning did not improv EMR children in agility balance and fine motor oordination. The question still remains only partially answered. What can be expected of the EMR and what type of physical education program will give optimal results.

PROCEDURE

As a means of tackling the local problem of retarded children the Cajon Valley School District, El Cajon, California, initiated a special physical education program in September 1969 as a pilot study

MATERIAL

The EMR subjects were 29 boys and 12 girls aged 6 1 to 1..5 years with I Q scores ranging from 50—80 on the WISC or Stanford Binet tests with a mean of 62 Initially the boys averaged 9 yrs 3 mos and the girls 9 yrs 2 mos Mean height and weight see Table 1

TRAINING

Physical training was conducted 30 minutes daily for six months All youngsters were enrolled in self-contained classrooms within the public schools. However the physical education was taught by specialists The physical education period had three components

(a) Warm-up developmental joint mobilizing, fitness, spacial 5—10 minutes
(b) Indi dual acti ties, i.e., trampolining, tumbling, jogging, rope-skipping, 10—20 minutes and
(c) Team acti ties e. Hawaiian football, soccer basketball, softball, and parachute play 10—20 minutes.

Table 1 EMR befor and after 6 month physical training Mean alues. Age 9

Variable		Girls Before	Girls After	Boys Before	Boys After
Height, in. (cm)		49 (125)	51 (129)	54 (137)	54 (137)
Weight, lbs (kg)		58 (26.5)	62 (28.3)	60 (31.3)	72 (32.9)
Pull Ups	No	6.5	14 8	0 62	1.32
Sit Ups	No	4.5	9.8	4 8	13.7
Grip, R & L, lbs (kg)		30 (13)	32 (15)	54 (24)	59 (27)
Std Broad Jump in (cm)		31 4 (80)	32.7 (83)	41 5 (105)	46 6 (118)
Shuttle Run	Sec.	16 8	15.8	14 4	13 6
50 yd Run	Sec.	13 0	12.5	10 9	9.8
Balance Beam	Steps	3 5	8.7	7.2	9 6
300 yd Run	Sec	124 2	100 2	88 1	78 2
12" Step Test	HR	114	129	111	117

Obstacle courses were used to challenge the youngsters. Following each daily physical education period, a relaxation phase was used to prepare the children for their return to the classroom.

TESTING METHOD

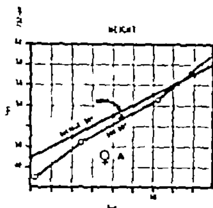
The first five of the test items used were from the Youth Fitness Test Manual (1) The girls used a modified pull-up technique. Additional 4 items included the balance beam walk, 300 yard run, right and left grip strength, and a three-minute step test (11)

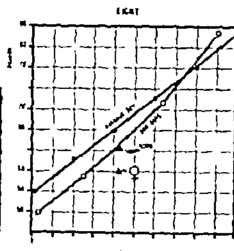
1 ( ) Pull-ups (boys) Overhand grip, full body hang, chin over bar, one trial, record total pull-ups
(b) Pull-ups (girls) Low horizontal bar overhand grip, knees flexed to 90° body parallel to floor, shoulders directly under bar arms fully extended, chest must touch bar, one trial, record total pull-ups
2 sit ps Straight knees, partner holds ankles, elbow touches opposite knee no resting, 30 second limit, one trial, record total sit ups
3. Standing Broad Jump Toe to front of starting mark, measure distance to heel, best of three trials, record in inches
4 Shuttle Run Two lines, A & B, 30 feet apart Two blocks 1 & 2, at line B Performer starts at line A, runs to B and picks up block no 1 returns and places block beyond line A, returns to line B, picks up block no 2 and returns to line A Best of tw trials, record in seconds
5 50 Yard Run Crouch start, 50 yd straight away one trial, measure in seconds.
6 Forward Balance Beam Walk (7) Beam width 2 inches, 9 inches from floor 12 foot length. Start with one foot on beam, alk in heel-toe manner across beam ithout mis-step for a total of 10 steps, no practice, record maximum number of steps of best of two trials
7 300 Yard Run (4) Course and turns marked with flags, one trial, record in seconds.
8 Three Minute Step Test (11) Bench height 12 inches, 30.5 cm, step rate 24/min duration three minutes sitting pulse count for one minute of recovery record one minute count.
9 Hand Grip, Right plus Left (7 10) Hand dynamometer, no practice, best of three trials, right and left hand, record in pounds.

RESULTS AND DISCUSSION

No increase was seen in the mean height of the boys. Body weight increased slightly from 31 3 kg to 32.9 kg. The girls showed an increase in height of four cm from 125 to 129 Their weight changed from 26.5 kg to 28 3 kg The girls were below the average in height and weight, while the older boys surpassed the average in both height and weight. The boys as a group remained within the a erage zone in both height and weight, while the girls also remained below average in both measurements (Fig 1)

In the area of strength, both boys and girls are below the norm. However they reach approximate the 53rd percentile. This is an appreciable ac complishment. There was a great variation in pull-ps, sit ups, hand grip, respectively (Fig. 2) Greater improvement occurred in pull-ups and sit ps than in hand grip The latter remained rela tively constant and very near to the mean of normal children. Table 1 gives the raw data for both sexes.





F g 1 Height and weight in educable mentally retarded (EMR) boys (=79) in comparison to normals.

It might be postulated that the EMR can compete with the normal in strength if they had the same degree of exposure to physical activity

In two power events, the 50 yard run and the standing broad jump, the EMR boys are at the 20th and 25th percentile, while the girls are much lower being at the 4th percentile in each. The shuttle run, an agility event, also finds the boys above the girls—25th as compared to the 9th percentile. In many games which require power and agility the EMR would be greatly handi capped.

Comparat e EMR data from Rarick et al (14) on the balance beam walk finds the Cajon Valley children above the mean. Boys scored at approximately the 60th percentile and the girls about the 55th percentile.

The 300 yard run is an inadequate measurement of endurance However a decrease in running time was observed in the boys from 88 1 seconds to 78.2 seconds (33rd percentile) Girls were observed at 1 1.2 to 100.2 seconds (4th percentile) The en durance as measured by the three minute step test gave the only negative results recorded. The recov ery heart rates (HR) increased in 30 cases, decreased in 10 and had no change in one subject. Thus HR increase occurred in 11 of the 12 girls. There appeared to be no age relationship. These results are unexplainable at this time.



F g 2 Mean percentile scores of physical different per formance tests in educable mentally retarded (EMR) boys (0) and girls (●)
Tests=1 300 yard run 2 50 yard run, 3 shuttle, 4.broad jump 5 pull ps, 6 sit-ups 7 hand grip 8 balance walk

In reviewing the results of the motor skill tests, it can be said that the EMR boys were superior to the girls, averaging about the 33rd percentile, and the girls the 22nd percentile Both EMR sexes were definitely inferior to normal children, but more nearly approached to the normal mean in strength than in the other parameters. One heartening trend was the improvement of both boys and girls in eight of the nine items after the training period. Perhaps with a longer exposure to physical edu cation a greater change may be observed.

Six boys of varying age were selected for the determination of max VO_2 The test, which is described elsewhere (1) was performed on a Monark bicycle ergometer using the Douglas Bag method Gas analysis was accompl shed by double

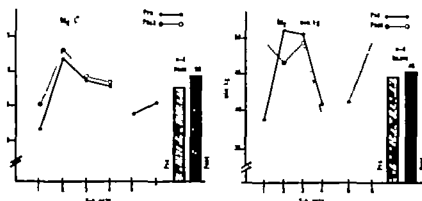


Fig 3 Maximal oxygen uptake in mentally retarded boys pre and post physical training.

determinations on the Scholander apparatus. Continuous ECG monitoring was accomplished, using a V5 lead. Each subject was given a preliminary practice period to acquaint him with the apparatus and method. Initial VO_2 was 1.68 l/min STPD or 45 4 ml/min/kg. (Fig 3) Only four subjects were available for re-testing after training. Little change occurred. The VO_2 went from 1 77 to 1 90 l/min, or 45 1 to 49 9 ml/min/kg in the four subjects. Maximum HR was 195 which is comparable to other workers as was $\dot{V}E$ at 65 l/min BTPS. The $\dot{V}O_2$ ranged from 6—19 % below that of the other workers. Mean values are given in Table 2.

SUMMARY

Educable mentally retarded children of both sexes in this investigation are below normal in strength, power agility and endurance skills A selected group of six EMR boys range 6—19 per cent below the mean of other workers in max VO_2, yet are within the normal range. The performance levels of the EMR children in this study are within normal range but below the 50th percentile. Physical training improved the result in most all the tests.

Table 2 Comparisons of maximal oxygen uptake ($\dot{V}O_2$) ventilation ($\dot{V}E$) and maximal heart rate between 6 educable mentally retarded (EMR) boys and normals

Group	V_{O2} STPD ml/min/kg	V BTPS L/min	Max HR/min
EMR	45 4	65 0	195
Astrand	56 2	63 5	196
Cumming & Morse	48 1	47 4	195
Robinson	52.0	53 4	198
Spyrnarov	49 7	—	197

REFERENCES

1 A. A. H. P. E. R., Youth Fitness Test Manual, Am Ass of Health, Phys Educ and Recrea, 1201 16th St., N.W Washington, D.C., 1965

2. Astrand, P O Experimental Studies of Physical Working Capacity in Relation to Sex and Age Munksgaard, Copenhagen, 1952.

3. C. A. H P E R Fitness-Performance Test Manual Can Ass Health, Phys Educ and Recrea, 1966.

4 Cumming, D E., & Morse, M., Cardiopulmonary Data for Child and Young Adult C. C. Thomas, Springfield, Ill., 1962.

5 Francis, R J and Rarick, G L. Motor Characteristics of the Mentally Retarded. Am J Ment Defic 63. 872, 1959

6 Geddes, D M. Effects of Mobility Patterning Techniques Upon Selected Motor Skills of Primary School Educable Mentally Retarded Children, Res Quart 39. 953, 1968.

7 Hart, M and Shay C. Relationships between Physical Fitness and Academic Success, Res Quart, 35 No 3 Part 2, 1964.

8 Howe, C A Comparison of Motor Skills of Mentally Retarded and Normal Children, Exc ptional Child 25 352, 1959

9 Ismail, A. H. The Effect of Well Organized Physical Education Program on Intellectual Performance, Res in Phy Educ 1 31, 1967

10. Johnson B. L., and J K. Nelson Practical Measurement for Evaluation in Physical Education Burgess Pub Co., Minneapolis, 1969

11 Kasch, F W A Comparison of the Exercise Tolerance of Post-Rheumatic and Normal Boys, J Assoc Phys & Mental Rehab 15 35—40, 1961

12 Kasch, F W Exercise Physiology Laboratory Man-

and San Diego State College, San Diego, Ca. 92115 1970
13. Keogh, J. F. Incidence and Severity of Awkwardness Among Regular School Boys and Educationally Subnormal Boys, Res Quart 39, 806, 1968.
14. Rarick, C. L., Widdop, J. and Broadhead, G. The Physical Fitness and Motor Performance of Educable Mentally Retarded Children, Except ional Child 36, 509 1970
15. Robinson, S. Experimental Studies of Physical Fitness in Relation to Age, Arbeitsphysiologie 10, 251 1938
16. Sprynarova, S. Development of the Relationship Between Aerobic Capacity and the Circulatory and Respiratory Reaction to Moderate Activity in Boys 11—13 Years Old, Physiologia Bohemoslovaca 15 53 1966.
17. Stein, J. The Potential of Physical Activity for the Mentally Retarded Child, J Health Phys Educ and Rec 37 35 1966.

(F.K.) San Diego State College
San Diego Cal 92115
USA

Key words: Mental retardation, physical fitness, physical training, maximal oxygen uptake, maximal heart rate, maximal ventilation.

Acta Paediat Scand Suppl 217 1971

PHYSICAL CAPACITY AND TRAINING IN A GROUP OF YOUNG ADULT MENTALLY RETARDED PERSONS

BENGT NORDGREN

From the ALA Foundation and the Department of Clinical Physiology University Hospital Uppsala, Sweden

Through the initiative of the ALA Council, a foundation for the mentally retarded, a group of young retarded persons (age 19—39 years, 39 men and 24 women) selected of those occupied in sheltered workshops for the mentally retarded, was studied. The aim was to investigate their potentialities for adaptation to a normal life (including industrial work and social activities)

The mental retardation constituted the dominating handicap (I Q values Terman Merrill 30 to 70) For up to three years the group was trained in industrial work, social activities and different sports, etc., by special personnel at the ALA Centre.

The actual *physical capabilities* were investigated by study of the *anthropometric data* measurements of the *isometric maximal muscular strength* and by *bicycle ergometry* (including heart rate, ECG blood pressure, respiratory frequency at rest and during standardized work load) For further description of the methods, see Nordgren (3)

ANTHROPOMETRIC DATA

The body built constitutes at least partially a prerequisite for the physical capabilities of an individual. It was therefore of interest to study some anthropometric data (which can give, among other things information about the skeletal development) Nordgren (1970 3) found no big differences from the normal series in mentally retarded men

To analyze the body build of the mentally retarded men in more detail they were divided into two groups educable (n=19 e.g. those able to benefit from the theoretical education of special schools for the mentally retarded) and non-educable (n=20)

The following data were recorded *medio-lateral width of* humerus at epicondyles, wrist, femur at condyles, ankle *length of* humerus, radius, femur tibia *circumference of* upper arm, forearm, thigh, calf chest, abdomen *body height body weight*

The anthropometric data for the non-educable men were expressed in per cent of those for the educable.

The means ($\bar{x}$) of these percentage values varied between 98 and 104 % No significant differences between the two groups were found.

Similar results were obtained in comparison between mentally retarded and normal women. Neither were any major differences found between the right and the left side in either sex (Nordgren, unpublished data)

MAXIMAL ISOMETRIC MUSCULAR STRENGTH

The isometric maximal muscular strength was tested in standardized body positions. The method used has earlier been described by Bäcklund and Nordgren (2) Much time and special care was

taken to help the patient to understand how to perform the tests, which is essential for the obtainment of satisfactory results.

When evaluating the muscular strength the same procedure was adopted as with the anthropometric data.

The values for the isometric maximal muscular strength in the mentally retarded men were found to be lower than in a normal material (3)

As in the analysis of the anthropometric data the mentally retarded men has been divided into two groups educable (n=19) and non-educable (n=20) Nordgren (4) He showed that the mean muscular strength ($\bar{X}$) in non-educable mentally retarded men was lower than educable.

Similar results were found in women. No appreciable differences between the right and the left side were found (Nordgren, unpublished data)

BICYCLE ERGOMETRY

Before the work test the group was examined medically for detection of diseases (especially in the circulatory system, which should always be done)

Successively increased submaximal loads (periods of 6 minutes) were applied and the work load at a heart rate of 170 beats/min (W_{170}) was used as an index of the work capacity Electrically braked bicycle ergometers were used because the mentally retarded had considerable difficulties in maintaining a prefixed rate of revolutions per minute on the bicycle, which is necessary when using mechanically braked bicycles Eight men were unable to carry out the test satisfactory for different reasons such as organic heart disease and subjective symptoms of tiredness and anxiety In some of the men there was discrepancy between the subjective experiences of exhaustion and the rather moderate objectively measured submaximal effort

The mean physical work capacity ($\bar{X}$) at W_{170} in those men who performed the test satisfactorily (n=31) was 1025 kpm/min The standard deviation (S) was 256 kpm/min This mean value does not differ from that in normal men The standard deviation is considerably higher however Thus, the work test showed considerable variation of work capacity (as judged from the standard deviation) within the group although the mean for the men who carried out the test was essentially the same as in healthy men. For further details, see Nordgren (3)

The measurements of the physical capabilities could also be utilized such that the physical training program could be carried out according to the capacity and limitations of each individual person within the group.

The study of the mean physical capabilities within the group thus showed

1 Ordinary body build.
2 Lower muscular strength than in normal persons (which was more pronounced in the non-educable)
3 A considerable variations of the circulatory functional capacity (some persons even unable to carry out the test)

PHYSICAL TRAINING

A program of gymnastic training (one hour twice a week for two months) was carried out in some of the subjects. Other mentally retarded persons without physical training served as controls. This consisted of circulatory training (i.e. running) coordination and muscular training. Music was used. Many of the men, but not all, liked different ball games. The results of the training program were expressed as the change in W_{130} from the initial value In this way each person could be tested against himself Thus in competition persons with low physical capabilities can improve most in percentage by increasing their degree of physical training which stimulates them.

A lower submaximal index (W_{130}) of the physical work capacity was chosen because of the considerable individual variation In this way all the trainees could be tested by using two lower submaximal work loads (men 300 and 600 women 200 and 400 kpm/min) This standardization was time saving and even the trainees with the lowest physical work capacity could carry out the test. These were great advantages, even though changes

in the heart rate due to anxiety for example, were probably of greater importance at this submaximal load than when W_{170} is used.

The physical work capacity (W_{130}) was about 30 % higher in the men after the training In the female group no appreciable difference was found. The variation in the results after the training was large It was difficult to activate the woman to more intense efforts during the training, which constituted a problem and could explain the difference in the results of training between the men and the women. In the male group the indi iduals w th the lowest initial work capacity (W_{130}) increased most in capacity indicating that persons with a low work capacity can show the best results of physical training These individuals probably also benefit most in their daily work and activities from a better physical performance. The physical training has been described in more detail (1)

REFERENCES

1 Andersson, S Bjórne, C., Collén, M., Elmeskog, A and Nordgren, B. Den utvecklingshämmades korppsliga förutsättning f r fysisk träning. *Psyksk ut ecklingshamning*, No 4 12, 1970.

2 Bäcklund, L and Nordgren, L. A new method for testing isometric muscle strength under standardized conditions. *Sc nd J Clin Lab I st* 21 33 1968.

3 Nordgren, B : Physical pabilities in group of mentally retarded adults. *Scand J Rehab Med* 2 125—132, 1970

4 Nordgren, B Isometric maximal muscular strength, physical work capacity and physical training in young adult mentally retarded persons. *Abstract I.A.S.S.M.D Congress* Warsaw 1970.

(B.N.) Dept. of Clinical Physiology
University Hospital
S-750 14 Uppsala
Sweden

Key ord Mentally retarded, physical capacity physical training

Acta Paediat Scand Suppl 217 1971

CORRELATIONS BETWEEN MUSCULAR STRENGTH AND INDUSTRIAL WORK PERFORMANCE IN MENTALLY RETARDED PERSONS

BENGT NORDGREN & LARS BACKSTROM

From th ALA Foundation, th Departm nt f Clinical Physiology th L   ty H p tal nd the D partm nt f P y iol gy Uni   ty f Uppsala S   d

An important task with mentally retarded persons is to place them in an occupation which they can manage without difficulties. With this goal in mind, a group of young adult mentally retarded persons, presented in a previous report (2) underwent evaluation, at the workshops of the ALA centre Uppsala, of their performance in industrial work.

It was considered of interest to determine whether this performance was influenced by muscular strength. In the present study measurements were therefore made of the isometric maximal muscular strength in essentially the same group of persons, and the different components of the test battery used were correlated, by multiple regression analysis, with their performance in ndustrial work.

The studies in this group were made on 4 male and 31 female persons, of ages 19—39 years, with different degrees of mental retardation

MUSCULAR STRENGTH:

The maximal isometric muscular strength was measured in standardized body positions using a Pressductor® transducer (2 and unpublished data)

Table 1 shows the maximal sometric muscular strength in the hand and the f ngers in educabl mentally retarded men (i   those able to benefit from the theoretical education of special schools for the mentally retarded) The lower number of subjects (n) for some of the test components is due to the fact that some men were unable to perform the test satisfactorily the abduction tests especially were found to be difficult for some of them. In order to determine whether a decrease in muscular strength had any relation to the degree of mental retardation the data in Table 1 (educable n = 3) were ompared with those for a group of non-educable mentally retarded men (n = 19) The female group consisted of 21 educable and 6 non-educable persons. The quotient (expressed in per cent) of the means ($\bar{X}$) for each test component between the non-educable and the educable mentally retarded persons was calculated. The mean quotients for each group of tests were then calculated for men and women separately The following results (X) were obtained

1 F earm hand men 91 % women 95 %

2 Fingers a opposition men 93   women 76 % b adduction men 79 % women 90 c abduction men 81

The alue for abduction in the women is not quite reliable as not all of the non-educable women were able to perform the tests.

Although the material was small, and the standard deviation considerable mean values < 100 % were found indicat ng that a higher degree of mental retardation is often accompanied by a lower muscular strength

Table 1 Maximal isometric muscular strength i the pper extremity in educable mentally retarded men (n=17 23)

	Right		Left	
	mean	S	mean	S
1 *Forearm-hand* (kpcm)				
Volar flexion, hand	66.4	25 0	67 3	26.1
Dorsal extension, hand	80 3	30 7	75 7	31.3
Pronation	60.1	27 0	57 1	24.9
Supination	54.2	20 5	58 0	22.1
Handgrip (kp)	38.9	14 0	38 4	13 3
2. *Finger* (kp)				
) Opp iti				
Digit I — Digit II	5 8	2 1	5 7	1 8
Digit I — Digit III	5 9	2 4	5 3	2 4
Digit I — Digit IV	4 4	2 1	4.2	2.2
Digit I — Digit V	3 1	1 3	3 0	1 4
b) Add cti				
Digit I — Digit II	6.7	1 7	6 0	2.1
Digit II — Digit III	2 9	1 7	2 6	1 3
Digit III — Digit IV	8	1 2	1 7	0.9
Digit IV — Digit V	1 5	1.2	1.5	0 8
) Abd ct				
Digit I — Digit II	1 5	0 6	1.5	0 6
Digit II — Digit III	1 5	0 6	1 8	0 6
Digit III — Digit IV	1 1	0 4	1 3	0 6
Digit IV — Digit V	1 4	0.6	1 5	0 9

PERFORMANCE IN INDUSTRIAL WORK

Evaluation of the performance in industrial work was made with the aid of two criteria 1) the prognosis group criterion and 2) the percentage group criterion.

Pr gnosis group Each trainee is allocated prognostically to different types of occupation (1) pure occupational therapy (2) work therapy (3) industrial therapy (4) sheltered workshop for the mentally retarded, (5) ordinary sheltered workshop or (6) work on the open labour market thus with better adaptation to working lif with in creasing f gures. This assessment is made by seven work supervisors, one psychologist and one occupational therapist, by ballot voting The assessment is made at a time point when each supervisor has had the trainee so long in his department at the workshop that he had had time to judge his or her practical potentialities for these different types of occupation. These types are referred to as prognosis groups (3) In the present group of trainees this assessment was repeated on two further occasions with good agreement.

Percentage gr up Another measure of the performance in industrial work is how much the mentally retarded person can produce i per cent of the mean value for an ordinary worker Such measures have often been used in industry and are applied in the workshop at the ALA-centre. For the present study the trainees were therefore divided into classes according to their industrial production. Class 1 corresponded to 0—15 %, 2 15—30 % 3 30—45 % 4 45—60 % 5 60—75 % 6 75—90 % and class 7 90—100 %. The assessment was made in the same way as for the prognosis group.

It was f considerable advantage for this study that the same work supervisors were able to assess the group of trainees over a long period of time (usually more than one year)

Correlations between muscular strength and performance in industrial work. At the ALA-centre the trainees are employed in different types of industrial work, which is part of their habilitation program.

The industrial work is generally not physically heavy. It was therefore not expected that very high correlations would be obtained between the values for muscular strength or for physical work capacity as measured by bicycle ergometry and the performance in industrial work. It was considered of value however to be able to predict the performance of these trainess in industrial work. Multiple regression analysis was therefore carried out. (The statistical treatment and the detailed results are presented in an appendix below). The prognosis group and percentage group criteria, respectively were correlated with the results of different tests of muscular strength and of the bicycle ergometry tests. From the statistical analysis it was of interest to note that the physical work capacity (W_{150} and W_{170}) was not selected as an important factor for the prognosis. As the industrial work was not very heavy this was to be expected.

The coefficients of correlation were not extremely high (0.73—0.82) but did explain more than two thirds of the variance when expressed as the reduction of the least squares.

The criteria are also, of course at least partially based on a subjective evaluation. Nevertheless, this type of assessment does provide a possibility for predicting the potentialities of the trainees in industrial work.

It is obviously important to make the greatest attempt to place the mentally retarded persons at an occupation where he will give his optimal performance.

REFERENCES

1 Nordgren, B. Physical capacity and training in a group of young adult mentally retarded persons. Acta Pediat Scand Suppl 217 119 1971
2 Nordgren, B. Physical capabilities in a group of mentally retarded adults. Scand J Rehab Med 125—132, 1970
3 Palmé R. Muscular fitness and work capacity in mentally retarded. Rapport 24 FUB Uppsala, 1969

(B N) Dept of Clinical Physiology
University Hospital
S-750 14 Uppsala
Sweden

Key words: Mentally retarded, muscular strength, industrial work

APPENDIX

The test components are presented in *Table II* where they are identified by the numbers in brackets. These numbers in brackets were used in the equations obtained in the multiple regression analysis. Muscles of the shoulders, the forearm and hand, the fingers, the legs (knee) and the trunk are represented. The physical work capacity (W_{130}, W_{170}) measured by bicycle ergometry (1) was also included in the regression analysis.

The variable with the highest correlation with the criterion (the prognosis or the percentage group) was first selected. The program thereafter selected the variable with the highest combined correlation for both variables with the criterion. This was done stepwise with successive introduction of new variables. In this way the initial coefficients of regression were changed when a new variable was introduced. If the correlation was not significantly higher ($p < 0.01$) the new variable was rejected.

Equations 1—6 show the results of the multiple regression analysis. The coefficient of correlation (R) and the standard error of estimate (S.E.) are given without and also with adjustment for degrees of freedom (adj f df).

In equations 1—4 only the values for the forearm-hand and finger tests were included because of the large number of variables compared with the number of subjects tested.

In *equations 5 and 6* the values for the shoulder, knee and trunk and the physical work capacity (W_{130}, W_{170}) were also taken into account. Because of the large number of variables in this second step of the analysis only those variables in the first step which were selected by the computer in *equations 1 and 2* could be included.

Table 2. Maximal isometric muscular strength

	The numbers within brackets are used in the equations for the respective test components				right	left
SHOULDER	Horizontal	pull	(kp)		/37/	/38/
		push	(kp)		/39/	/40/
	Vertical	pull	(kp)		/41/	/42/
		push	(kp)		/43/	/44/
FOREARM—HAND	Volar flexion		(kpcm)		/27/	/28/
	Dorsal extension		(kpcm)		/29/	/30/
	Pronation		(kpcm)		/31/	/32/
	Supination		(kpcm)		/33/	/34/
	Handgrip		(kp)		/35/	/36/
FINGER	Opposition		(0.1 kp)	Dig. I—II	/ 3/	/ 4/
				Dig. I—III	/ 5/	/ 6/
				Dig. I—IV	/ 7/	/ 8/
				Dig. I—V	/ 9/	/10/
	Adduction		(0.01 kp)	Dig. I—II	/11/	/12/
				Dig. II—III	/13/	/14/
				Dig. III—IV	/15/	/16/
				Dig. IV—V	/17/	/18/
	Abduction		(0.01 kp)	Dig. I—II	/19/	/20/
				Dig. II—III	/21/	/22/
				Dig. III—IV	/23/	/24/
				Dig. IV—V	/25/	/26/
KNEE	Flexion		(kp)		/45/	/46/
	Extension		(kp)		/47/	/48/
TRUNK	Forward flexion		(kp)		/55/	
	Back ward extension		(kp)		/56/	
PHYSICAL WORK CAPACITY		W_{130}	(kpm/min)		/57/	
		W_{170}	(kpm/min)		/58/	

MEN (n = 12)

Prog[illegible] group [illegible]on
([illegible] 1)

y_1 = −0.023 /36/ −0.015 /4/ +0.009 /25/ −0.039 /5/ +0.019/9/ −0.006 /21/
+0.029 /15/ −0.033 /16/ +0.015 /6/ +0.016 /31/ +0.036 /35/ +0.018 /10/
+0.003 /25/

R = 0.81 (adj [illegible] df = 0.73)

SE = 0.71 (adj [illegible] df = 0.83)

Perc[illegible] [illegible]terion
([illegible] 2)

y_2 = +0.012 /36/ −0.056 /7/ +0.008 /21/ +0.05[illegible] /9/ −0.033 /5/ +0.017 /14/
−0.010 /26/ +0.010 /30/ −0.005 /19/ +0.007 /21/ +0.015 /31/ +0.005 / 5/ +0.008 /50/

R = 0.83 (adj. [illegible] df = 0.76)

SE = 0.85 (adj [illegible] df = 0.98)

WOMEN (= 31)

Pr[illegible] group [illegible]te
([illegible] 3)

y_3 = +0.065 /10/ +0.021 /25/ −0.013 /23/ −0.001 / 6/ −0.092 /30/ +0.193 /36/
+0.052 /14/ −0.037 /35/ −0.070 /16/

R = 0.85 (adj [illegible] df = 0.80)

SE = 0.62 (adj [illegible] df = 0.72)

P[illegible] [illegible]terion
([illegible] 4)

y = +0.052 /10/ −0.010 /1/ +0.029 /25/ −0.012 /23/ +0.013 /20/ +0.011 /14/
−0.058 /9/ +0.135 /36/ −0.017 /35/ −0.031 /30/ −0.006 /21/ +0.041 /7/ −0.011 /13/

R = 0.89 (adj [illegible] df = 0.80)

[illegible]E = 0.58 (adj [illegible] df = 0.[illegible]4)

MEN ([illegible]12)

Pr[illegible] group [illegible]te
([illegible] 5)

y = +0.010 /38/ −0.034 /3/ +0.010 /23/ +0.034 /9/ −0.005 /21/ +0.008 /36/
+0.005 /21/ +0.014 /36/ −0.017 7/ +0.009 /31/

R = 0.84 (adj [illegible] df = 0.78)

SE = 0.66 (adj [illegible] df = 0.75)

Percentage [illegible]te
([illegible] 6)

y = +0.050 /36/ −0.056 /7/ +0.011 /21/ +0.084 /39/ −0.048 /5/ +0.078 /9/
−0.006 /26/ +0.035 /36/ +0.005 /23/ +0.014 /30/ −0.010 /19/ −0.173 14/
+0.023 /6/ −0.068 /37/ +0.079 /43/

R = 0.89 (adj [illegible] df = 0.82)

SE = 0.76 (adj [illegible] df = 0.93)

Acta Paediat Scand Suppl 217 1971

MUSCULAR METABOLISM AND PHYSICAL EXERCISE

G HARALAMBIE

From Medizinische Universitätsklinik Freiburg/Breisgau Germany

Discussing the problem of the metabolism of skeletal muscle during physical exercise, one encounters right from the beginning several difficulties. The first of these arises in considering the notion of *muscle*. Already three centuries ago, white skeletal muscles, differing from red ones, were described in animals by STEFANO LORENZI (1678) thus introducing a first distinction *which has been in the meantime* well supported for human muscles too (3 28 30, 46) On the other hand, since the late twenties papers have been published which give strong support to the assumption that the metabolic response of muscles previously "trained to heavy physical loads considerably differ from that of normal, i.e. untrained muscles.

The second difficulty concerns the concept of *metabolism*. The meaning of this term is well known however the tendency exists to speak merely of the energy metabolism of the muscle cell, some times overlooking such important aspects like the trophic metabolism, the highly complicated neuro-endocrine regulation and secondary changes induced by physical activity. In this respect, rather few indirect and incomplete data are found, which indeed do not *facilitate* our understanding of these phenomena.

The third difficulty arises in dealing with the term *exercise*. The problem of the different metabolic changes occuring under different conditions of exertion is still under investigation. The presently known facts however allow the statement that one could not speak about the effects of exercise in general but only about changes observed under strictly defined conditions of exertion. The nature, intensity duration and repetition of the exercise stimuli are in this respect of major importance.

Once these points mentioned are kept in mind one could try to discuss some features *concerning* the biochemical changes—particularly in the muscles—following physical exercise.

The main metabolic task of the working muscle is the resynthesis of its direct energy-supplying source which is, as well known, ATP. Hultman *et al* (26) showed that the ATP content of the human quadriceps muscle amounts at rest to about 2.5 mmoles per 100 gr of dry tissue. Meanwhile, only part of the ATP is available for the direct use in the contraction-relaxation process. Another part is indirectly used for the energy supply i.e. in the transformation of phosphorylase *b* into the *a* form, in the phosphorylation of glucose and of fructose-6-phosphate, in the activation of the free fatty acids, etc. Finally ATP is needed in the cell for maintaining the labile protein structures. This *explains why only a* part of the ATP is used in the muscle for the performance of mechanical work. In fact, Hultman *et al* (25 26) found that even after heavy exertion, the concentration of ATP in muscle falls only to about 40 % of its resting value.

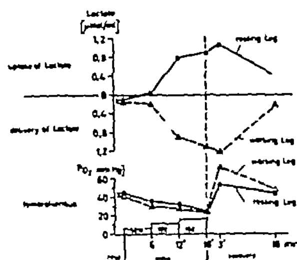


Fig. 1 Changes in the arterio-femoral venous difference of lactate and in the femoral venous oxygen pressure in subjects working on the bicycle ergometer (... f g (8)

The maintenance of a definite level of ATP in spite of the high rate of its breakdown implies a rapid resynthesis which takes place at first over the reaction catalysed by the enzyme ADP phosphocreatine phosphoryl transferase. It could be assumed that the energyrich phosphate bond of phosphocreatine is the main source of energy for the types of exercise where the duration does not exceed 15 to 20 seconds. It was shown that the phosphocreatine content of the working muscles decreased proportionally to the work load, very low end values being attained (6)

Other energy-sources for the resynthesis of ATP during short lasting work are muscle glycogen and blood glucose. In conditions of acute need for ATP the breakdown of carbohydrates occurs over the anaerobic glycolytic pathway

It is generally assumed that for the energy production via glycolysis the muscle mainly relies upon its glycogen reserve. The glucose content of the muscle cell is in fact low it depends on the plasma glucose level and on the permeability of the muscle-cell membrane to free glucose, which is in turn *insulin-dependent*. As concerns the influence of insulin it should be mentioned that several authors failed to find under various experimental conditions, a rise of this hormone in plasma during exercise in man (33 37 42)

Blood glucose levels of athletes at rest do not differ from those of untrained persons (28) In both groups, as well as in animals, the glucose uptake from the arterial blood by the muscle, and consequently the arterio-venous difference were found to be increased during exercise at submaximal intensity (8 38, 38) Meanwhile other workers failed to observe this rise of the A V difference of glucose, both in animals with tetanized muscles and in humans (4, 11) *It might be that the rate* limiting step of the glucose uptake by the muscle, i.e. phosphorylation, is influenced by the inhibitory effect of the increased concentration of glucose-6-phosphate on hexokinase (4) an accumulation of this product was found in mouse and rat muscles after short-duration tetanus (1 12) It also could be that the disagreement between the findings of various authors is explained by the different parameters of exercise and experimental conditions.

During exercise of stepwise increasing *intensity* the arterial blood glucose level slightly but significantly decreases (27 28) a *tendency to rise* towards the resting level can be seen at the end of the exertion. That non working muscles could deliver glucose to the blood during exercise seems very improbable (15 15) On the other hand, there exists evidence of a marked increase of the glucose output in the hepatic vein (25 40) which suggests that liver glycogen also serves as substrate for the working muscles. However a marked breakdown of muscle glycogen always takes place if definite conditions of work intensity and duration are fulfilled this occurs even if glucose is supplemented to the exercising subjects (5)

It was mentioned above that anaerobic glycolysis only occurs under acute need for ATP resynthesis. At a low work intensity the lactate formed is oxidized pyruvate and further in the Krebs cycle this happens not only in working muscles but also in the resting ones and in the heart (Fig 1) Thus a marked rise in blood lactate will be found only at a definite work intensity this lies higher in trained than in untrained subjects (20, 28)

The consideration that anaerobic glycolysis is not *necessarily bound to a cellular hypoxia, but rather* to a disturbance of the balance between the requirement for ATP and its aerobic resynthesis, seems to be stressed by several facts (27 28) At a femoral venous oxygen pressure of 23 Torr an increased output of lactate from the muscles was found during exercise in untrained subjects, but the same could not be observed in athletes who *extracted* lactate from arterial blood. Furthermore, at a maximal work load, resulting in the lowest values of venous pO_2, the lactate/pyruvate ratio in the venous blood is lower than in arterial blood, *which obviously speaks against "true muscular* hypoxia. Eventually several factors contrivute to a better oxygen supply to the working muscles during heavy exercise, such as the increase in the temperature of the muscle, the increase of hematocrit, the decrease of the blood pH and the dilatation of the arterioles.

Several years ago, Volkow attracted attention to the different changes in blood lactate level, if different types of interval work are performed. Thus, if repeated runs of 200 m., with 70 % of the maximal speed are performed with pauses of *2 to 3 min., a high oxygen uptake is rapidly* attained while the lactacidaemia, initially also high, begins to decrease after the third run. If however, 400 m. runs are performed, at continually shortening intervals (e.g 6 5 4 min.) after an initial rise, the oxygen consumption begins to diminish, while blood lactate attains very high levels. Similar patterns of blood lactate during two variants of interval load were described by Keppler *et al* (27) In Fig 2, an exampl is shown of a different evolution of lactacidaemia in children aged 13—14, after several 30 m. runs, with different length pauses (50) On the basis of his data, Volkov discussed the possibility of the occurrence during hard, repeated work of the Crabtree effect, i.e. the inhibition of the oxydative processes by the anaerobic glycolysis (47 48) This hypothesis is not definitively proved, but offers an interesting perspective of research.

The rise of muscle and therefore also of blood lactate, brings into activity several mechanisms di-

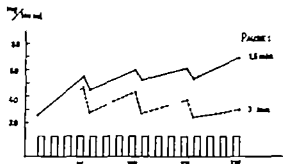


Fig 2. Changes in blood lactate during successive 30 m. runs with variable pause intervals in 13 to 14 year old boys (50) Roman numerals show the number of the run.

rected against this phenomenon. It is worthy to mention that the first "brake of the lactic acid formation in the muscle is perhaps lactate dehydrogenase itself The distribution of the LDH isoenzymes is different in white and in red muscle fibers of humans (46) red muscle fibers are rich in the I and II forms, which are inhibited by an excess of lactate, particularly if the pH is also low (43, 44) Besides, the whole lactate dehydrogenase activity is much higher in the predominantly white muscles than the red ones (3 30) both in humans and animals.

There are also other mechanisms at the cellular level which could contribute to the delayed formation of lactic acid. During the oxidation of pyruvate, intermediate metabolites of the Krebs cycle are formed, someof which were found to accumulate in the muscle during work (6, 41) It is known that phosphorylase *a* and *b* are inhibited by malate, whereas the activity of phosphofructokinase is lowered by comparatively low levels of citrate (34, 35) If the key rôle of the latter enzyme is considered, it may be assumed that these facts have a physiological importance it must be remembered that as result of the fatty acid oxidation, more acetyl-coenzyme A and consequently more citrate are formed in the muscle during exercise. The intermediate products of the citrate cycle also could be implied in the dilatation of the arterioles in muscle during the earlier stages of exertion, probably owing to their ability of "blocking free calcium ions (16)

It was shown that the longer the duration of

an exertion—and thus the lower its intensity—the lower also was the blood lactate of the exercising subjects (–, 1). This is not only due to a diminished anaerobic breakdown of carbohydrates or to an enhanced oxidation of pyruvate, but also to the fact that muscles use fatty acids as a fuel during long lasting exercise.

At the start of work, a fall of the plasma free fatty acids is observed, together with their increased uptake by the muscle. This fall is only transient (8) being followed by a rapid rise brought about by the enhanced mobilization of fats and consequent lipolysis. As a result of the release of FFA from the triglycerides, glycerol markedly increases in plasma after several hours of exercise (22). Several enzymes implied in the metabolism of glycerol were found in muscles, e.g. glycerokinase in the myocardium (39) glycerol-dehydrogenase in the diaphragm (45) and a glycerol metabolizing system in the human quadriceps muscle (5). However this substrate is quantitatively of minor importance.

The contribution of the muscle lipids to the energy metabolism is very probably not unimportant. However there are presumably species differences, as well as much influence of food intake. Moreover differences exist in this respect between red and white muscles, the former containing more neutral fats and free fatty acids, as well as fat metabolizing enzymes than the latter (28).

The main part of fatty acids which the muscle uses as energy source derive from lipids of nonmuscular origin (28) the control of the lipid mobilization from the adipose tissue is activated by several mechanisms, such as catecholamine-induced lipolysis growth hormone release which is increased in man during exercise (42) and also by not well-clarified nervous influences (9). Lipids mobilized from the adipose tissue are for the major part split into glycerol and FFA and oxidized but if the exercise lasts long enough (e.g. one hour or more) an increase of the total blood serum lipids is found, which suggests that the rate of their mobilization may be higher than that of their breakdown. Moreover if athletes are examined at rest after several days of training, significantly higher blood lipid levels are found in long-distance runners, cyclists and skiers, as compared with boxers and sprint runners.

Theoretically the FFA are completely oxidized to water and carbon dioxide however products of the incomplete degradation of fatty acids are found in increased amounts in the blood serum (10 32) —3 hydroxybutyrate and acetoacetate—and even in the expired air—acetone—(49) at the end and shortly after a long lasting exertion. The rise of the blood ketone bodies is by far less apparent in trained than in untrained men (10).

Data of Keul *et al.* (29) show that physical training in man results in a higher lipid mobilization and lipolysis together with an enhanced utilization of FFA in the working muscles.

In animal experiments, Molé and Holloszy (31) found that after a training period, muscle homogenate has a significantly higher capacity to oxidize palmitate to CO_2. The activity of several enzymes implied in this process in such trained animals is almost double as compared to untrained controls. Thus, the trained organism can use fatty acids better than the untrained i.e. it derives a higher percentage of its energy from the fatty acid oxidation and this oxidation is more complete.

There is still uncertainity concerning the utilization of amino acids as a fuel by the muscle during exercise. The patterns of the arterio-venous differences of the various amino acids are dissimilar thus tryptophan and glutamic acid are retained whereas alanine and glutamine are released by working muscles (?8). Even if it is assumed that the extracted amino acids are used in the energy production—which is far from being proved—the quantities implied would be low enough not to be important.

Physical training is a strong stimulus for the muscle protein synthesis, which finally results in muscle hypertrophy. Decreased protein degradation and increased biosynthesis were found in work induced hypertrophy after tenotomy in rats (17). The "trained" muscles have significantly higher amounts of myoglobin (36) and mitochondrial protein (1) as compared to untrained. If the intensity and/or the duration of exercise are in

adequately high, biochemical changes were described in animals (23) and especially in man (7 19 20 21) which seem to suggest that degradation processes preponderate. In young boys and girls aged 12 to 15 a marked rise in the urinary elimination of creatinine, ethanol-precipitable hexoses (19) tyrosine and indole-derivatives (18) were found even several hours after heavy exercise (swimming, boxing and athletic training) However in children following an adequate training program, an increase in total serum proteins as well as in the electrophoretically determined Albumin/Globulin ratio were observed. This could be considered as a suitable response to exercise, since in overstrained adult athletes, both total serum proteins and A/G ratio are significantly lowered (20)

It is sometimes very difficult to connect these and other changes in the blood composition and renal elimination to the metabolism of the muscle cell *stricto sensu* nevertheless, these phenomena are also consequences of muscular work and have presumably multiple influences on the muscular metabolism, thus being of interest for the muscle physiologist.

REFERENCES

1. Arese, P Kirsten, R and Kirsten, E Metabolitgehalte und -gleichgewichte nach tetanischer Kontraktion des T abenbrustmuskels und des Rattenmuskels *Biochem Z* 341 523 1965
2. Astrand, P-O Hallback, I Hedman, R and Saltin, B Blood lactate after prolonged severe exercise. *J Appl Physiol* 18 619 1963
3. Bass, A Brdiczka, D Eyer, P Hofer S and Pette, D Metabolic differentiation of distinct muscle types at the level enzymatic organization *Europ J Biochem* 10. 198, 1969
4. Bergström, J and Hultman, E The effect of exercise on muscle glycogen and electrolytes in normals *Scand J Clin Lab Inv st* 18. 16, 1966
5. Carlson, L Lipid metabolism and muscular ork *Feder Proc* 26 1755 1967
6. Chagovets, N. Changes in the citric and oxaloacetic acid content of the muscle during recovery after exercise (russian) *Confer Instit...* p 92, Leningrad 1963
7. Chailley Bert, P Plas, F and Pallardy G Le metabolisme protidique au cours de l effort prolongé *La Pres Med.* 70 705 1962
8. Chapler C., and Stainsby W.. Carbohydrate metabolism in contracting dog skeletal muscle in situ. *Am J Physiol* 215 995 1968.
9. Cobb, L., Ripley H., and Jones, J Role of the nervous system in free fatty acids mobilization as demonstrated by hypnosis. *In.* M. Karvonen and A. Barry (ed.) *Physical activity and the heart* Ch. Thomas, 1967 Chapter 16.
10. Corbett, J Johnson, R., Krebs, H Walton, J and Williamson, D The effect of exercise on blood ketone-body concentration in athletes and untrained subjects. *J Physiol* 201 83, 1969
11. Corsi, A., Menotti, M and Granata, A. L.. In situ utilization of glycogen and blood glucose by skeletal muscle during tetanus. *Am J Physiol* 216. 1534, 1969
12. Costill, D. Metabolic responses during distance running. *J Appl Physiol* 28. 251 1970.
13. Danforth, W and Lyon, J. Glycogenolysis during tetanic contraction of isolated mouse muscles in the presence and absence of phosphorylase *a*. *J Biol Chem* 239. 4047 1964.
14. Doll, E., Keul, J and Maiwald, C.. Oxygen tension and acid-base equilibria in venous blood of working muscle. *Am J Physiol* 215 23, 1968.
15. Dulin, W and Clark, J Studies concerning possible humoral factor produced by working muscles. Its influence on glucose utilization. *Diabetes* 10. 289 1961
16. Frölich, E Vascular effects of the Krebs cycles intermediate metabolites. *Am J Physiol* 208. 149 1965
17. Goldberg, A. Protein turnover in skeletal muscle. I. Protein catabolism during work-induced hypertrophy and growth induced with growth hormone. *J Biol Chem* 244. 3217 1969
18. Haralambie, G. Date asupra metabolismului unor ammoacizi in efortul fizic. *Cult fiz si Sport* 17 (2) 52 (1964)
19. Haralambie, G. Biochimie si Sport, ed. U.C.F.S., Bucarest 1966.
20. Haralambie, G Valeurs biochimiques sériques et syndrome de super sollicitation chez le sportif *Acta Biol Med Germ*, 17 34, 1966.
21. Haralambie, G., and Keul, J Beziehungen zwischen Proteinstoffwechsel und körperlichen Belastungen. *Med Welt* (in press)
22. Havel, R., Pernow B., and Jones, N.: Uptake and release of free fatty acids and other metabolites in the legs of exercising men. *J Appl Physiol*, 23 90, 1967
23. Highman, B and Altland, P Effects of exercise and training on serum enzyme and tissue changes in rats *Am J Physiol*, 205 162, 1963

24. Holloszy J Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J Biol Chem 242*: 2278, 1967

25. Hultman, E. Studies on muscle metabolism of glycogen and active phosphate in man with special reference to exercise and diet. *Scand J Clin Lab Invest 19 Suppl 94*, 1967

26. Hultman, E Bergstrom, J and McLennan Anderson, N. Breakdown and resynthesis of phosphoryl creatine and adenosine triphosphate in connection with muscular work in man. *Scand J Clin Lab Invest 19*: 55 1967

27. Keppler D Keul, J and Doll E. The influence of the form of exercise on the arterial concentrations of glucose, lactate, pyruvate and free fatty acids. *In* J. Poortmans (ed.) *Biochemistry of Exercise* Medicine and Sport Vol. 3 S. Karger Basel—New York, 1969

28. Keul, J Doll, E and Keppler D *Muskelstoffwechsel* J. A. Barth, München, 1969

29. Keul, J Doll, E., and Haralambie G Freie Fettsäuren, Glycerin und Triglyceride im arteriellen und femoral venösen Blut vor und nach einem vierwöchigen körperlichen Training *Pflügers Arch 316*: 194, 1970.

30. Kleine, T Enzymmuster gesunder und pathologisch veränderter Muskeln des Menschen. *Z Klin Chem Klin Biochem 5*: 214, 1967

31. Molé, P and Holloszy J Exercise-induced increase in the capacity of skeletal muscle to oxidize palmitate to $^{14}CO_2$. *Proc Soc Exper Biol Med 134*: 789 1970.

32. Neumann, G Basch, G Lorenz, R Schuster, H.-G Senger, H., Hotz, G., Taubmann, W and Kaiser R., Scharschmidt, F Untersuchungen von Kreislauf und Stoffwechselparametern während und nach einer einstündigen Belastung mit einem Renarad auf einem gebremsten Rollengerät (Home-trainer) *Wiss Zeitschr Dt Hochsch Körperkult* (Leipzig) *10*: 59 1968

33. Nikkilä, E., Taskinen, M R., Miettinen, T Pelkonen, R and Poppius, H.. Effect of muscular exercise on insulin secretion *Diabetes 17* 209 1968

34. Parmeggiani, A and Bowman, R Regulation of phosphofructokinase activity by citrate in normal and diabetic muscle *Bioch Biophys Res Commun 12*. 268, 1963

35. Passonneau, J., and Lowry O The role of phosphofructokinase in metabolic regulations *Adv Enz Regul 2*: 265 1964.

36. Pattengale, P and Holloszy J Augmentation of skeletal muscle myoglobin by a program of treadmill running. *Am J Physiol 213* 783, 1967

37. Pruett, E.. Glucose and insulin during prolonged work stress in men living on different diets. *J Appl Physiol 28* 199 1970

38. Reichard, G Issekutz, B Kimbel, P Putnam, R., Hochella, N and Weinhouse, S. Blood glucose metabolism in man during muscular work. *J Appl Physiol 16*. 1001 1961.

39. Robinson, J and Newsholme, E.. Glycerol kinase activities in rat heart and adipose tissue. *Bioch J 104*. ., 1967

40. Rowell, L., Masoro E and Spencer M.. Splanchnic metabolism in exercising man. *J Appl Physiol 20*. 103., 1965

41. Sacktor, B Wormser-Shavit, E., and White, J.. Diphosphopyridine nucleotide-linked cytoplasmic metabolites in rat leg muscle in situ during contraction and recovery *J Biol Chem 240*. 678, 1965.

42. Schalch, D The influence of physical stress and exercise on growth hormone and insulin secretion in man *J Lab Clin Med 69* 256, 1967

43. Schwert, G Miller B and Peanasky J.: Lactic dehydrogenase X. A reevaluation of the effects of pH upon the kinetics of the reaction. *J Biol Chem 242*: 3425 1967

44. Stambaugh, R and Post, D Substrate and product inhibition of muscle lactic dehydrogenase heart (H_4) and muscle (M_4) isoenzymes. *J Biol Chem 241* 1462, 1966.

45. Toews, C. Evidence for the metabolism of glycerol by skeletal muscle and the presence of a muscle NADP-dependent glycerol dehydrogenase *Biochem J 98*. 27 1966.

46. Van Wijhe M., Blanchaer M., and St. George Stubbs, S The distribution of lactate dehydrogenase isozymes in human skeletal muscle fibers. *J Histochem Cytochem 12*. 608, 1964.

47. Volkov N Influence of the pause interval duration on the training effect by repeated physical exercise (russian) *Teoria Prakt Fiz Kult* p. 552, No. 2, 1964

48. Volkov N Die Wechselbeziehungen zwischen Atmung und Glykolyse bei Muskelarbeit verschiedener Leistung *Med Sport 4* 44, 1964.

49. Walther A and Neumann, G. Über den Verlauf der Azetonausscheidung in der Ausatmungsluft bei Radsportlern vor während und nach einer spezifischen Laborbelastung *Acta Biol Med German*, .2: 117 1969

50. Yakovlev N Kaledin, S Krasnova, A., Leshkevits, L., Popova, N Rogozkin, V Chagovets, N and Kuritsin, A Physiological and chemical analysis of adaptation to brief intensive muscular activity in adolescents *Fiz J SSSR, 48*. 1105 1962.

(B.H.) Medizinische Universitätsklinik
7800 Freiburg im Breisgau
German Federal Republic

PHYSICAL ACTIVITY BY ADOLESCENTS

JOHN V G A DURNIN

From Institute of Physiology The University Glasgow Scotland

This paper gives a brief tentative summary of some results which we have obtained in studies of the food intake and energy expenditure by adolescents in the city of Glasgow Scotland. The prime purpose of the studies was to investigate the nutritional status of these adolescents, so the principal measurement was of the food intake by the children. The investigation was done in 2 parts. In the first, measurements were made on 102 boys and 90 girls aged between 13 and 15 years and attending eight different schools in the city of Glasgow This period was between January 1963 and June 1965 The nutritional results obtained provided almost the only detailed information available on adolescents in the UK for that period and, because of the possibility that the nutritional status of children and adolescents had altered in the interim, we are presently engaged on a repeat study of somewhat similar nature, on a larger group of adolescents also living in Glasgow This second study began in March of this year and will attempt to cover 600 adolescents. So far we have measured just under 200 subjects and results of an interim nature are being presented here on just half of that group—i.e. about 100 boys and girls.

In the earlier study detailed measurements were made, during a period of seven consecutive days, of the energy expenditure of the children, as well as their food intake, so that we have very precise knowledge of exactly how these children spent their time and we made many measurements of energy expenditure in all of the different activities of the day We can thus give fairly accurate information about the energy output, not only in separate activities such as walking or sitting or playing games, etc., but also total daily energy output. In the present investigation however we were unable, because of smaller numbers of staff to include precise and detailed measurements of energy expenditure, and we have restricted ourselves to obtaining a rather simplified account of how the time was spent by the children in four categories of activity i.e. 1) while they were in bed, 2) while sitting and standing, 3) while doing work involving minor degrees of movement (designated *moderate activity*) and 4) while doing more strenuous forms of exercise—such as walking moderately fast, or playing any game or doing any physical work which would be considered as higher than moderate It is important to stress that a comparison between the two studies, from the point of view of physical activity can not be precisely made because of the different groupings of the activities.

In both studies the children came from all of the different social groups. The purpose of the present paper is to make some comparisons of the amount of physical activity indulged in by these children, and how this relates to body build and the number of people in the household. Body build was assessed from the skinfold thickness at four sites, (over the biceps and triceps muscles, and at the subscapular and supra-iliac regions) From previously published work (2) we are able, from these skinfold thicknesses, to give an approximate value for the total fat content of the body of these adolescents. We have therefore roughly sub-divided the boys and girls into those who are moderately slim, those of an intermediate build, and those who are slightly plump. The percentages of fat in these separate groups are shown in the tables 5 and 6.

Table 1 gives the age, height and weight of the

Table 1 *Some Physical Characteristics of the Glasgow adolescents (1963—1965)*

	Boys	Girls
	102	90
Age (yrs)	115 ±0 1	115 ±0 5
Height (cm)	163 ±10	159 ±6
Weight (kg)	51 ±10	52 ±8

Table 2. *Energy intake and expenditure of the Glasgow adolescents (1963—1965)*

Social class	Intake (kcal/day) Boys	Girls
I	2950	2 30
II	860	2270
III	660	2400
IV	2770	2500
Intake $\bar{X}$	2795 ±190	
Expenditure $\bar{X}$	2650 ±440	

adolescents in the earlier study and table gives values for food intake and energy expenditure by social group.

Table 3 shows the effect of different sizes of households, and I think it is fairly obvious that there seems to be little observable influence exerted by size of household on this particular measurement.

The amount of time spent by the boys in physical activity of various categories of heaviness was related to body build. Unfortunately in that first study we did not have a sufficient number of boys whom we classified as fat or plump to provide a separate group so that there is no difference between the thin and the intermediate group (by body build) in relation to their physical activity either as the average for the day or while just at school. However there is an indication that there may be a social influence—perhaps surprisingly in that the boys from the poorer social groups are apparently more active than those from the more wealthy households, although the facilities, at school and otherwise, for the children from the more economically privileged households were better than those for the poorer groups.

Among the girls there was a sufficient number

Table 3 *Energy expenditure (kcal/day) of adolescents related to number of persons in household*

	No. of persons 3	4	5	6	6+
Boys	638	603	2619	2565	2651
Girl	318	2270	2251	346	22

of fat girls to form a separate group and it appears that they are significantly less active than the thinner girls. Again, there is the same difference between social groups. The amount of the decreased activity of the fatter girls seems to be related to their leisure time activity as one might suspect since they are more regimented in school and must equally participate in exercise and games. However Bullen *et al* (1) have shown a rather interesting facet of the effect of body build on activity since even when the fat children are apparently active they spent longer being inactive, while participating in games, than the non-obese.

Table 4 shows some average times and energy expenditures of adolescents in different activities. There is no significant difference between the boys and the girls in the duration of these activities. But there is a very large individual variation in the amount if time spent in moderate and heavy activity Thus the range of energy expenditures in moderately heavy activity can be seen to cause differences of over 200 kcal/day between different boys and just over 1000 kcal/day between different girls. Clearly this variation in activity is reflected by the large differences found in the total energy expenditure of individual adolescents.

Tables 5 and 6 relate to the present survey The data are from approximately equal numbers of boys and girls, roughly 30 children in each group. The first of these tables shows the amount of time spent in bed and while sitting and standing, subdivided for the different body builds. It seems clear that there is neither a difference within the sexes relative to body build, nor is there a difference between the sexes whether one is fatter or thinner than average, whether one is a boy or girl, therefore made little impact on the amount of time spent on these inactive activities

Table 4. Average daily times (min) and energy expenditure (kcal/day) of adolescents at different [illegible]

		Bed	Sitting and standing	Standing activity	Moderate and heavy activity
Boys		575 (611)	531 (793)	117 (370)	183 (852)
	Range	463—739	331—668	20—280	57—395 (16—2863)
	C.V %	9	11	28	47
Girls		583 (565)	481 (613)	194 (459)	155 (574)
	Range	468 787	68—608	66—446	55—314 (186—1[illegible]87)
	C.V %	8	14	38	44

Values in parenthesis.

The last table gives similar information related to activities involving movement. There are some peculiarities in the results, the significance of which is at present uncertain and which may well alter when results on larger numbers of subjects are accumulated. Superficially it seems unusual that, in the case of the boys, the thinner group seem to be less active both in moderate and heavy activities than the fatter group. Although for the girls, these results are not exactly duplicated there would seem to be little difference between the three subdivisions of body build for moderate and heavy activities.

It is unfortunate it is not possible to make a precise comparison between the amount of physical activity of the adolescents in 1963—65 and those of the present day. One factor which has altered slightly is the fat content of these children, which was 16 % of the body weight for the boys in 1963—65 and 18 % today and 26 % for the girls 1963—65 and 28 % today. This may be significantly related to a change in physical activity.

Table 5. Number of minutes per day spent in bed and sitting and standing by adolescents, subdivided for body build in % fat

		Overall mean	I	II	III
			15 %	16—20 %	21 %
Boys	Bed	567	572	563	570
	Sit/Stand	634	650	628	629
			I 24 %	II 25—30 %	III 31 %
Girls	Bed	579	575	586	[illegible]
	Sit/stand	641	656	621	[illegible]

Table 6. Number of minutes per day spent in moderate and heavy activities by adolescents subdivided for body build in % fat

		Overall mean	I	II	III
			15 %	[illegible]	[illegible]
Boys	Moderate	165 ±78	[illegible]	[illegible]	172
	Heavy	101 ±51	[illegible]	[illegible]	[illegible]
Girls	Moderate	190 ±[illegible]	[illegible]	[illegible]	
	Heavy	61 ±[illegible]	[illegible]	[illegible]	

REFERENCES

1. Bullen, B. A., Reed, R. B. and Mayer, J. *Amer. J. Clin. Nutr.* 14, 211, 1964.
2. Durnin, J. V. G. A. and Rahaman, M. M. *Br. J. Nutr.* 21, 681, 1967.

Key words. Physical activity, adolescent girls and boys, caloric, Energy Intake & Expenditure

BODY COMPOSITION IN CHILDREN: A REFERENCE STANDARD FOR MAXIMUM AEROBIC POWER OUTPUT ON A STATIONARY BICYCLE ERGOMETER

C T M Da ies

F m th Medical Resea ch Coun il Physiology Res ar h U it Lo d School of Hygiene nd T pi al Medici e Lond E gland

The maximum aerobic power (V $_2$ max) is an effective measure of the combined capacities of the cardiovascular system to transport, and the working muscles to utilise oxygen. For this reason is has formed the basis of many tests particulary in children of exercise capacity but there is still little agreement on how V $_2$ max should be expressed.

In many situations where one is simply interested in either total work output or the ability of the child to move his body weight, then the expression of $\dot{V}_{O_2}$ max in absolute (l/min) or relati e (ml/kg/min) terms is entirely appropriate. However in comparative studies where one is interested in the detection of functional limitations of children from different ethnic and en ronmental background, one cannot ignore the influence of body size and composition on performance. This is particulary true when one uses the bicycle ergometer where body weight is supported, to measure V$_{o^2}$ max d rectly

MATERIAL AND METHODS

In the present study which forms part of a larger nvestigation of the physical working capacity of British children (Davies, Barnes & Godfrey to be published) we have measured 116 boys and girls aged 6—16 yrs during maximum effort on a bi cycle ergometer On a separate occasion various measurements of body size and composition were taken These included body weight, height, skin fold thickness at 3 sites, thigh calf and leg vo-

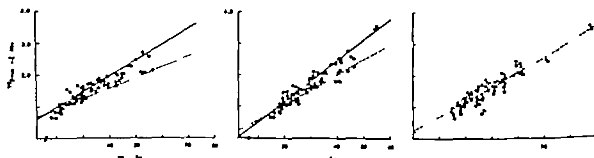


Fig 1 Maximal oxygen uptake ($\dot{V}$ $_2$ma) in relation t body w ght (Wt) to lean body mass (LBM) calculated from body weight and skinfold thickness and t Limb lume (LV) = calf + thigh volume by water displacement. O = girls, = boys

lume (corrected for fat) by water displacement (1 2) These latter parameters have been shown to be closely correlated to actual muscle mass de termined by soft tissue radiography (2)

RESULTS

The results are summarised in fig 1 Maximum aerobic power is related to body weight and to lean body mass but the variance about the regression line is large and a sex difference is apparent. How ever when $\dot{V}_{O_2}$ *max is related to limb volume* (LV — thigh & calf volume) the inter subject va riation is reduced and the sex difference disap- pears. Indeed LV accounts for more than 80% of the total variance of V_{O_2} max in this group of children.

These results suggest that (1) the V_{O_2} max in children is related to amount of muscle which can be brought into use and in cycling this is essentially the muscles of the leg (ii) the lower V_{O_2} max of the girls is due mainly to their smal ler (leg) muscle mass and (iii) in comparative bicycle ergometer studies of power output in child ren there is a need to relate V_{O_2} max to leg size and composition and to standardise for these be fore determining the finer details of cardiorespira tory performance.

REFERENCES:

1 Cotes, J E, Davies, C.T.M., Edholm, O. G Healey M. J and Tanner, J M. Factors relating to aerobic ca- pacity of 16 British males and females ages 18—28 years. *Proc Roy Soc B Lond* 174, 91 1969

2 Jones, P.R.M Pearson, Jean. Anthropometric deter mination of leg fat and muscle plus bone volumes in young male and female adults J Physiol. 204, 63—64P 1970

(C D) Environmental Physiology Unit
London School of Hygiene
Keppel Street, W C.1 London, England

Key words Body composition, maximal oxygen uptake, limb volume, girls and boys 6—16 years.

SHORT TIME EXERCISE AND NUTRITIONAL STATUS IN ETHIOPIAN BOYS AND YOUNG MALES

NILS-HOLGER ARESKOG

From the Department of Clinical Physiology, Regional Hospital, Linköping, Sweden

In the discussions of the long range unfavourable effects of malnutrition the important factors are not so much deviations from normal of anthropometric variables, such as height, weight and skinfold measurements, but rather the *functional* performance of the body i.e. expressed as capability to perform physical and mental work.

In this communication I will briefly give you some of the results from a physical fitness study in Ethiopia, performed at the Ethio-Swedish and Children's Nutrition Unit (CNU) in Addis Ababa. The intention was to map the physical fitness situation in better and worse nourished groups of children and young adults.

METHODS

Physical fitness tests. A standardized work test on bicycle ergometer with stepwise increased loads was performed up to exhaustion. W_{170} was calculated. This value is an index of maximal work performance (capacity during short time exercise). Furthermore pulmonary function tests and muscle strength tests of five muscle groups were made. The summed strength of these muscle groups was taken as a muscle force index.

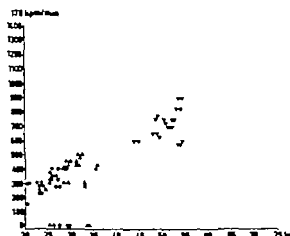
We intended to determine the maximal oxygen consumption, but the mouthpieces were not popular during maximal work and we had to give up these plans to be able to perform the study with the intended material. However, I do know that professor Lange-Andersen from Oslo succeded in a later study to determine the maximal oxygen consumption in a material from the northern region of Ethiopia, but these data are—as far as I know—still not published.

Also a clinical status, including anthropometric and skinfold measurements, routine blood, urine and stool parasites tests was performed. An interview by a nutritionist was made and included a 24 hours recall and a questionnaire for estimating frequency of using different food items. The consumption calculations were based upon the detailed studies within the frame work of the CNU project, thus increasing the accuracy of the nutritional data.

The subjects were carefully informed about the investigation to get a good cooperation. To increase the motivation for the tests we made especial physical fitness medals for the best in every group and served refreshments after the test.

MATERIAL

There were three groups representing the less well nourished part of the material. Groups 1 and 2 consisted of 86 boys from a public school, 9—11 and 12—14 years old respectively. Group 5 consisted of 42 young shoe factory workers. The better nourished part of the material was represented by groups 3, 4 and 6 consisting of 67 boys from a private school, 9—11 and 12—14 years old respectively and 50 cadets from the Imperial Ethiopian Air Force.



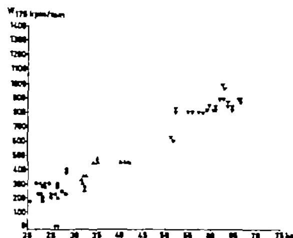


Fig 1 and 2. Correlation of physical work performance measured as W_{170} kpm/min and body weight. Dots at zero value represent children who could not work long enough to reach pulse value that could be extrapolated to 170. Symbols: ● grp 1 public school, 9—11 yrs △ grp 2, public school 12—14 yrs ▼ grp 5 shoe factory workers, 18—25 yrs ○, grp 3, private school, 9—11 yrs ▲ grp 4 private school, 12—14 yrs ▽ grp 6, air force cadets, 18—22 yrs.

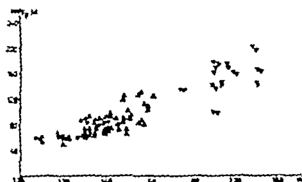
RESULTS

The caloric values were low for all groups, expect for the cadets. The mean values were group 1 1750 group 2, 2095 group 3 2200, group 4, 2350, group 5 2400 and group 6, 3500 Kcal. The main energy source in groups 1—5 consisted of carbohydrates, as is typical in developing countries. There was a high intake of iron due to contamination of the ironrich soil in the main staple teff. However, the absorption of this iron is probably limited. In groups 1 2 and 5 the retional intake is very low. The ascorbic acid intake is low in all groups except for the cadets. However the boys from the private school showed mainly higher values than those from the public school. Quantitatively the protein intake was sufficient, but qualitatively unsatisfactory in the bad nourished groups. The detailed analysis of the nutritional results of this work is given elsewhere. (1)

Considering the bodyweight there was a difference in weight between the cadets and the shoeworkers averaging 5 kilos. After checking the military files I found that the cadets had gained just about 5 kilos during their first year in the air force in spite of the military physical training. This indicates the order of magnitude of weight difference between the well nourished and the bad nourished young male Ethiopean. The weight to

Table 1. Mean values of height, weight, physical work test (W_{170}), maximal voluntary ventilation (MVV) and muscle strength

Group	Height cm	Weight kg	W_{170} kpm/min	W_{170}/weight kpm/min/kg	MVV l/min	Muscle strength index
1	133.4 ±6.0	[illegible]6.3 ±3.1	3148 ± 90.0	12.0	68.9 ±10.8	58.[illegible]
2	141.7 ±5.9	31.8 ±3.9	3785 ± 99.6	11.9	86.9 ±19.3	69.4
3	131.6 ±5.6	25.5 ±2.8	2518 ± 76.3	9.9	65.4 ±13.6	56.0
4	147.7 ±7.5	34.8 ±5.8	3568 ± 94.6	10.2	89.9 ±22.9	75.6
5	168.7 ±5.7	54.0 ±5.9	7170 ±117.8	13.3	166.3 ±39.1	123.2
6	170.2 ±7.2	58.6 ±6.3	8250 ±153.8	14.1	177.9 ±33.6	143.2



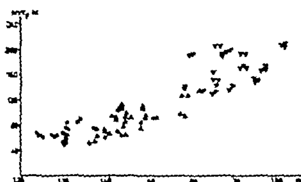


Fig 3 and 4 Correlation of maximal voluntary ventilation (MVV) and height.
Symbols as in Fig 1.

height values indicate a slender body building The skinfold values (triceps, scapula and abdomen) are in all groups lower than for Western age mates. The Hb-values—corrected for altitude (2,300 metres above sea level) according to Hofvander (3)—are slightly but not significantly lower than Western standards.

The results of *physical fitness studies* are presented in Table 1 and Fig 1—4. W_{170} is compared to Western age mates somewhat low However calculation W_{170} per kilo bodyweight gives another situation. *In spite of an often very inadequate diet* the Ethiopian children are then in the same order physical capability as Western age mates and adults only slightly lower The children in the public school perform more than their better nourished colleagues in the private shool, but this *might depend on a higher degree of* physical activity and training In the private school the children usually were fetched by cars while the public school children had to walk and run often very long distances every day and they seemed to have a higher physical activity during playing at school too.

In contrast to the results of the work test on the bicycle ergometer the older private school children had a slightly better muscle strength than the older public school children. The cadets were also better than the shoe workers. Perhaps both better nutrition and more advanced prepubertal development contribute to this difference

Regarding some of the respiratory values maximal voluntary ventilation (MVV) was on an average slightly lower in the shoe workers group than in the cadets group (166±39 l and 173±34 l respectively) The children do not remarkably differ from from swedish age and height mates (2) Like these the MVV values were well correlated to height (Fig 3—4)

Correlating the food intake versus the physical work capability (W_{170} and muscle strength) was correlated by dividing the material into subgroups after more or less than 75 % of the WHO/FAO recommended intakes (4, 5 6) regarding calories, calcium and ascorbic acid no significant differences between the groups were found.

DISCUSSION

The influence of malnutrition on physical fitness might work in two ways.

1 Permanent stunting of growth as a consequence of severe malnutrition in childhood. All our groups except parts of the children from the private school could have been influenced by this factor

2 The relative hyponutrition throughout life might decrease the prerequisites for physical activity and decrease e g storage of muscle glycogen creating a risk for an untrained circulatory and muscular apparatus. This factor may have influenced our bad nourished adult groups.

In our material two factors probably tend to underestimate the physical work capacity

Firstly the altitude—Addis Ababa is namely situated on 2,300 metres (7 000 feet) above sea level and even if these individuals are fully acclimatized, their sea level response to exercise might be better according to earlier figures in the literature. However recent reports from different parts of the world have shown that the sea level response for fully acclimatized high altitude natives is not remarkably different from their high altitude response.

Secondly for almost all of the individuals it was the first time of biking, so the coordination between muscle groups was not the best during the first minutes of biking. However after some minutes these difficulties were overcome by most of the boys.

CONCLUSIONS

In spite of often very inadequate diets, the physical capability measured by three different method was surprisingly good in these Ethiopian boys and young males. No correlation between individual bad nutrition and physical work performance was found. However this investigation perhaps ought to be supplemented with long time exercise studies, before we make any definite statements of too high recommended minimum requirements in the FAO/WHO tables. However, the definition of these requirements and allowances warrant further discussion regarding e.g. physical activity—a global problem in a world of increasing shortage of food.

REFERENCES

1 Areskog, N. H., Selinus, R., and Vahlquist, B. Physical work capacity and nutritional status in Ethiopian male children and young adults. *Am J Clin Nutr* 22. 471, 1969

2 Bjure, J. Spirometric studies in normal subjects. *Acta Paed Scand* 53 232, 1963.

3 Hofvander, Y. Hematological investigations in Ethiopia with special reference to a high iron intake. *Acta Med Scand* Suppl 494, 1968.

4 FAO Nutritional studies. Calorie requirements. Rep no 15 Rome, 1957

5 Joint FAO/WHO Expert Group. Calcium requirements. *WHO Techn Report Ser* no. 230, 1962.

6 Recommended Dietary Allowances. *Nat Acad Sci Nat Res Counc P M*, 1146, Washington, D.C., 1964.

(N. H. A.) Dept. of Clinical Physiology, Regional Hospital, 581 85 Linköping, Sweden.

Key words. Physical fitness, malnutrition, schoolboys, factory workers.

THE EFFECTS OF REPEATED PROLONGED EXERCISE ON PLASMA GROWTH HORMONE, INSULIN GLUCOSE, FREE FATTY ACIDS, GLYCEROL, LACTATE AND β-HYDROXYBUTYRIC ACID IN 13-YEAR OLD BOYS AND IN ADULTS

BENGT O ERIKSSON, BENGT PERSSON and JAN I THORELL

From the Department of Paediatrics Karolinska Institutet, St Görans Children's Hospital, the Department of Physiology, Gymnastik- och Idrottshögskolan, Stockholm and the Isotope Laboratory General Hospital Malmö Sweden

Growth hormone (GH) has been claimed to play a central role in the regulation of the utilization and storage of body energy sources. However many of the specific effects of GH have not yet been clarified, and it has been shown that a variety of factors can trigger an increase in the release of GH. Examples of specific factors are hypoglycemia (4, 3 31) and hyperaminoacidemia (2, 1) stress (7) and muscular work (10 13 14, 17 22, 28) are nonspecific factors.

A series of experiments were made to study the interrelationship of GH in the metabolic adjustment to hard, muscular work. The first experiment is reported on here. It deals primarily with work induced release of GH in relation to spontaneous diurnal changes in plasma GH (15) Because of differences in the effects of GH on growth at different ages, both rapidly growing children and adults were included in the series.

MATERIAL AND METHODS

Four healthy men, 23—34 years, and four healthy boys, 12—13 years, were examined. Fig 1 shows the schedule for the two-day experiments in which "Day 1" consisted of a control period differing from "Day 2" only in the omission of the two exercise periods. After an overnight fast, subjects had a standardized breakfast consisting of 1 teacup of a Swedish infant formula (Semper) 100 Calories. A catheter was inserted into the brachial

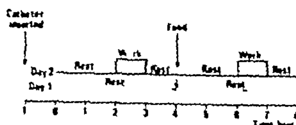


Fig 1 The experimental procedure Day 1 four hours of rest, then a standardized meal followed by another four hours of rest Day 2, the same procedure except for two periods of exercise lasting for one hour each, two and six hours after the onset of the experiment

artery Subjects rested for one hour before starting the trial.

Exercise consisted of one hour's work on a mechanically braked bicycle ergometer at a mean load of 63 (range 55—73 %) of their maximal oxygen uptake. This had been carefully determined earlier using the levelling off criterion. Expired air was collected in Douglas bags, and gas samples were analyzed by the Haldane Technique (1) During the hour of work, double determinations were made of oxygen uptake about 15 and 45 minutes after the start of work. Heart rate was taken every tenth minute. Urine was collected for the total eight hour period both days and analyzed to cathecholamine content

Blood was collected every tenth minute during the eight hour period for radio-immunological assay of GH and insulin (30 31) and enzymatical

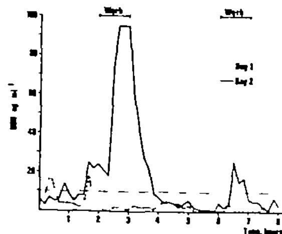


Fig. 2. GH level in one of the subjects during eight hours of rest (dashed lines). The solid lines sho the GH-level when standardized exercise periods were included tw and six hours after the onset of the experiment.

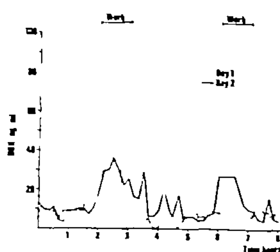


Fig. 3. GH level in one of the subjects during rest (dashed line) and when exercise periods were included (solid line). The striking increase in plasma level of GH during day one could not be explained.

determination of lactate (27), glucose (12), glycerol (19) and β hydroxybutyric acid (β HBA) (3) and colorimetric determination of free fatty acids (20).

RESULTS AND COMMENTS

Control experiments. During the 8 hour control period with continuous rest, only interrupted by the standardized meal, the plasma GH level on Day 1 stayed at a mean level of 10 g/ml (range 4.4—20.6). The mean value for the 8 subjects during this eight hour period was 10.0 ng/ml (range 2.8—13.3). The standardized meal did not change GH level. A slight but not significant difference was found between the four adults and the four boys, i.e. 8.7 g/ml (range 2.8—13.3) and 11.4 ng/ml (range 9.4—12,9) respectively. Two of the boys showed very distinct peaks (Fig. 3) in irregular occasions which could not be attributed to any exogenous factor.

The occurrence of such sudden rises in the release of GH has been described earlier especially in children and during sleep (29). However these peaks make the evaluation of GH in certain experimental situations difficult and emphasize the importance of adequate control studies. No consistant changes in heart rate or in the excretion of cathecolamines, were found to explain these pronounced peaks.

Work experiments. Resting levels on the second day of the study were similar to the first days. The periods of exercise raised plasma GH levels strikingly. Two typical cases are shown in Figs. 2 and 3. The mean levels in GH during the exercise periods proved to be rather constant with a mean value of 48.9 ng/ml (range 39.9—55.5) for the first exercise period and 70.5 ng/ml (range 13.7—43) for the second. No typical pattern was found in the GH increase, and the highest value obtained for the individuals was reached at different intervals from the onset of the work. Nor was any difference found between adults and the boys. After cessation of work I the GH level decreased, reaching a mean level under 10 ng/ml 30 minutes after work (8.9 ng/ml). The same pattern was found after work II, although level under 10 ng/ml (9.4 ng/ml) was reached only 30 minutes after the cessation of work.

As seen in Fig 4, exercise induced a distinct increase in plasma glycerol levels. Changes in FFA were more variable and displayed a smaller increase than glycerol. This is probably due to variations in the uptake of FFA by the tissues (8, 11). As in previous studies (6, 9) a postexercise in-

Acta Paediat Scand Suppl 217 1971

THE EFFECTS OF REPEATED PROLONGED EXERCISE ON PLASMA GROWTH HORMONE, INSULIN GLUCOSE, FREE FATTY ACIDS, GLYCEROL, LACTATE AND β-HYDROXYBUTYRIC ACID IN 13-YEAR OLD BOYS AND IN ADULTS

BENGT O. ERIKSSON, BENGT PERSSON and JAN I THORELL

From the Department of Pediatrics, Karolinska Institutet, St Goran's Children's Hospital, the Department of Physiology, Gymnastik- och Idrottshögskolan, Stockholm and the Isotope Laboratory, General Hospital, Malmö, Sweden

Growth hormone (GH) has been claimed to play a central role in the regulation of the utilization and storage of body energy sources. However many of the specific effects of GH have not yet been clarified, and it has been shown that a variety of factors can trigger an increase in the release of GH. Examples of specific factors are hypoglycemia (4, 25 31) and hyperaminoacidemia (2, 21) stress (7) and muscular work (10, 13 14, 17 22, 28) are nonspecific factors.

A series of experiments were made to study the interrelationship of GH in the metabolic adjustment to hard, muscular work. The first experiment is reported on here. It deals primarily with work induced release of GH in relation to "spontaneous" diurnal changes in plasma GH (15). Because of differences in the effects of GH on growth at different ages, both rapidly growing children and adults were included in the series.

MATERIAL AND METHODS

Four healthy men 23—24 years, and four healthy boys, 12—13 years, were examined. Fig 1 shows the schedule for the two-day experiments in which "Day 1" consisted of a control period differing from "Day 2" only in the omission of the two exercise periods. After an overnight fast, subjects had a standardized breakfast consisting of 1 teacup of a Swedish infant formula (Semper) 100 Calories. A catheter was inserted into the brachial artery. Subjects rested for one hour before starting the trial.

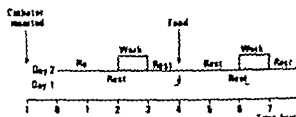


Fig 1 The experimental procedure. Day 1: four hours of rest, than a standardized meal followed by another four hours of rest. Day 2: the same procedure except for two periods of exercise lasting for one hour each, two and six hours after the onset of the experiment.

Exercise consisted of one hour's work on a mechanically braked bicycle ergometer at a mean load of 63 (range 55—73 %) of their maximal oxygen uptake. This had been carefully determined earlier using the levelling off criterion. Expired air was collected in Douglas bags, and gas samples were analyzed by the Haldane Technique (1). During the hour of work, double determinations were made of oxygen uptake about 15 and 45 minutes after the start of work. Heart rate was taken every tenth minute. Urine was collected for the total eight hour period both days and analyzed to cathecholamine content.

Blood was collected every tenth minute during the eight hour period for radio-immunological assay of GH and insulin (30, 31) and enzymatical

Acta Paediat Scand Suppl 217 1971

HORMONAL AND METABOLIC CHANGES DURING AND AFTER PROLONGED MUSCULAR WORK IN PRE PUBERTAL BOYS

SVEIN OSEID & LARS HERMANSEN

From P diat Research I stitut Uni ersity Hospital, Rikshospitalet and Institut of Work Physiology, Oslo, Nor ay

Carbohydrate and fat are utilized as fuel for the energy yielding processes during muscular work, while protein plays a non-essential role (4) The relative contribution of carbohydrate and fat to the total energy metabolism during exercise is dependent on several factors, such as diet, intensity and duration of work and the physical fitness of the subjects (5 13)

Both carbohydrate and fat metabolism are subject to hormonal control during exercise (12, 21 26, 28) and exercise is also known to elicit changes in the secretion of some of these hormones. Human growth hormone (HGH) and norepinephrine are known to increase during exercise in adult subjects (9 17 18, 31 36) while plasma immunoreactive insulin (IRI) decreases during prolonged exercise regardless of duration and intensity of the work (26, 27) However growing individuals might exhibit different or exaggerated patterns of response, and surprisingly few studies have been concerned with the effect of exercise on hormonal elease and metabolic changes in children.

In connection with a longitudinal study (1968—1970) on various effects of prolonged exercise in pre-pubertal boys we had the opportunity of studying some of the hormonal and metabolic changes during and after prolonged exercise. The purpose f the present in estigation was to study the changes in free fatty acids (FFA) in serum and plasma glucose concentrations during and after prolonged severe exercise (i.e. treadmill running for 1 hour at approximately 70 % of the individual's maximal oxygen uptake) in pre pubertal boys, and furthermore to investigate the behaviour of plasma IRI and plasma HGH in relation to plasma glucose and serum FFA, respectively

MATERIAL AND METHODS

The study was performed on 23 pre-pubertal boy from the same class in one of the schools in Oslo. They were studied for three consecuti years from the time they ere 10 5 years old (mean age) The metabolic studies, however hav been carried out only during the last tw years, 1969 and 1970. All subjects were healthy at the time of investigation without major handicaps or illnesses One boy with familiar hypercholesterolemia was included in the study the others had no metabolic diseases

The boy reported t the laboratory 1,5 hour after light breakfast (2 small sandwiches and glass of milk) and rested for at least another hour before the exercise. The resting oxygen uptake as measured during the last 5 minutes of the rest period. A polyethylene catheter was introduced approximately 15 cm into the antecubital vein in the 1970 study and resting blood sample was withdraw The catheter was kept patent using 3 1 % sodium citrate In the 1969 study the blood samples were taken by venepuncture shortly before work and at the 5 th minute of the recovery period.

The subjects ran on motor driven treadmill (3 inclination) for 60 min at speed of approximately 70 % of the individual maximal oxygen ptake The choice of speed of the treadmill during the prolonged exercise was determined by previous tests

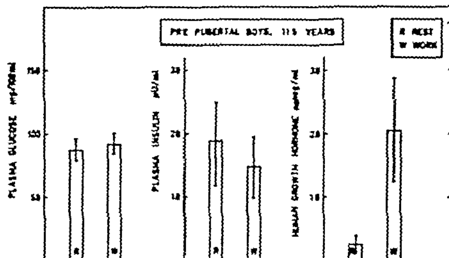


Fig 1 Mean values and standard deviations for plasma glucose, plasma IRI and plasma HGH in 23 pre-pubertal boys before and 5 min after 1 hour treadmill running representing on an average 67 % of the individual maximal oxygen uptake.

Oxygen uptake was measured three times during the exercise period, i.e. at 20, 40 and 60 min. Blood samples were withdrawn into glass syringes at 20, 40 and 60 min of the exercise period, and at 5, 15, 30 and 60 min of the recovery period. The blood samples were immediately transferred to ice-cold tubes and centrifuged in refrigerated centrifuge. The plasma and serum were drawn off into test tubes and that which was not immediately analyzed was stored in the freezer. All blood samples were analyzed for plasma glucose using the method of Hultman (16), plasma IRI by the double precipitation technique of Hales and Randle (10), serum FFA was titrated according to the method of Dole and Trout (34) and serum immunoreactive HGH was analysed using the radioimmunoassay procedure of Norman and Turter (25). All determinations of HGH were performed at The Hormone and Isotope Laboratory, Aker Hospital, Oslo. Maximal oxygen uptake was measured according to the procedure suggested by Hermansen and Saltin (14) and the expired air was analyzed in duplicate using Scholander gas analyzer.

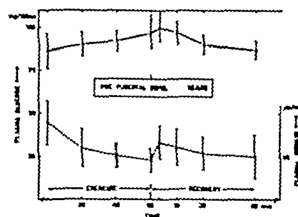


Fig 2 Mean values and standard deviations for plasma glucose (upper panel) and plasma IRI (lower panel) in 23 pre-pubertal boys before, during and after 1 hour treadmill running representing on an average 71.4 % of the individual maximal oxygen uptake.

RESULTS

The work load in the 1969 study varied between 58 and 76 % (mean 67 %) of the individual's maximal oxygen uptake, with an average oxygen uptake of 1.45 liter/min (SE = 0.04). The average oxygen uptake in the 1970 study was 1.80 liter/min (SE = 0.06) representing on an average 71.4 % (65.7—78.2 %) of the maximal oxygen uptake.

In the 1969 study (Fig 1) there was no significant change in plasma glucose levels before and after work, e.g. the initial level was 88 mg/100 ml as compared to 91.7 mg/100 ml 5 min after work stop. In 14 boys there was a slight increase, and in 9 boys a slight decrease in plasma glucose.

The plasma IRI level fell from a mean value of 18.9 µU/ml after work, i.e. a fall to approximately 80 % of the pre-exercise value. A decrease was found in 17 of the boys, while 6 boys showed an increase in IRI levels after work. The increase, however, was significant in only 3 boys.

The mean values and the standard deviations for the plasma glucose and plasma IRI in the 1970 study are shown in Fig 2. Plasma glucose increased

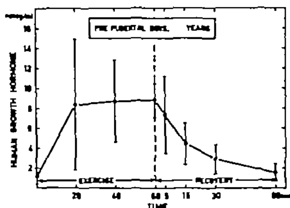


Fig 3 Mean values and standard deviations for plasma HGH in 23 pre-pubertal boys before, during and after 1 hour treadmill running representing on an average 71 4 % of the individual's maximal oxygen uptake.

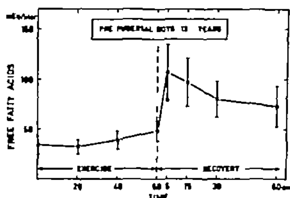


Fig 4 Mean values and standard deviations for FFA in serum in 23 pre-pubertal boys before, during and after 1 hour treadmill running representing on an average 71 4 % of the individual's maximal oxygen uptake.

slowly but steadily from an initial level of 86 mg/100 ml to 97 mg/100 ml by the end of exercise representing a 12 % increase. There was also a small increase during the first 5 minutes of the recovery period followed by a steady fall untill the *initial level was reached after 60 minutes. 4 boys* showed a slight decrease from the initial level during the first 20 minutes of work, while another 2 boys exhibited essentially unchanged plasma glucose levels throughout the whole period of exercise.

The normal glucose/insulin relationship was changed *during exercise in that increasing plasma* glucose levels were not followed by an increase in plasma IRI In fact, the IRI levels decreased from an initial value of 17.8 µU/ml to 9 1 µU/ml after 60 min of exercise The greatest fall was observed during the first 20 min of exercise, which accounted for approximately 70 % of the total fall. The IRI level *increased in the recovery* period with a maximal level at 5 min, followed by a slow fall throughout the 60 min of recovery These changes were rather consistent in the whole group

The initial HGH level in the 1969 study was 2.6 nanog/ml which increased by approximately 8 times to a mean level of 20 6 nanog/ml (Fig 1)

The HGH response in the 1970 study (Fig 3) was brisk and long lasting, with a 7 5 fold increase from the resting value to the value obtained immediately after work stop. There was a gradual fall after the work stimulus had ceased, however, the value at 60 min after work stop was still above the resting value. The standard deviations at 20 min and 40 min at work are very high indicating a very different pattern of response, e.g. brisk *responders* and slow responders.

The FFA response in the 1970 study (Fig 4) showed a slight, but insignificant fall over the first 20 min of work from an initial level of 0.34 mEq/l to 0.32 mEq/l, followed by a small increase to 0 39 mEq/l after 40 min and to 0.48 mEq/l after 60 min of exercise. After work stop where was a *rapid* increase in FFA *during the first 5 min of* recovery to a mean value of 1.07 mEq/l, followed by a steady fall over the next 25 min (0 97 mEq/l after 15 min, 0.80 mEq/l after 30 min) then levelling off to 0 73 mEq/l after 60 min. Thus the values remained high during the whole recovery period, and did not fall to the initial level.

The individual levels differed very little *during* work. A fasting level above 0.50 mEq/l was found in only two boys, both of whom exhibited a quick fall during the first 20 min of exercise with increasing values thereafter The increase after work stop was significant in all the boys studied, with a maximal mean value at 5 min in the recovery period in 20 out of 23 boys. In the other boys the peak value was reached 15 30 and 60 min after work stop.

DISCUSSION

Immunoreactive HGH was found to increase by approximately 6 to 8 times above the pre-exercise level during prolonged severe exercise in pre pubertal boys. Although the relative work load was approximately the same in both studies (i.e. 1969 and 1970) the HGH response was somewhat more pronounced in the 1969 study The increase of HGH during prolonged exercise is in good agreement with earlier reports in adults (17 30)

Several workers have been concerned with the nature of the HGH stimulating factor(s) during exercise (2, 3 8 18) Sutton *et al* (33) showed that increased blood lactate concentration caused by exercise or lactate infusion elicited an increased release of HGH. In the present study however blood lactate concentration was found to increase only slightly and there was no consistent relationship between the HGH response and the blood lactate concentration In this investigation only one work load (i.e. 70 % of the individual s maximal oxygen uptake) was performed in each subject each year It might well be that increasing work loads which also give rise to an increasing lactate production (1) would elicit subsequent greater release of HGH.

An initial transient hypoglycemia has been proposed as a possible stimulus to HGH secretion during exercise (18) In this study however no hypoglycemia was observed. On the contrary a slight increase in plasma glucose was obtained in most subjects during the work period. One would also expect a hypoglycemic stimulus to be rather pronounced to give any persistent HGH secretion (31)

The initial pre-exercise levels of HGH were consistantly low 3 hours after a l ght breakfast. The values obtained after 20 and 40 min of exercise showed large inter individual variations, while the HGH level at the end of the work per od (i.e. 60 min) was high and showed a much smaller standard deviation when compared with the levels at 20 and 40 min of work.

It is well known that several factors nfluence the HGH level during resting conditions (8 22 23 30 33) and large flucturations ha e been reported during the course of a 24 hours period (7 19 20) Although these observations might explain part of the large inter individual differences after 20 and 40 min of exercise, they could hardly explain the consistent increase which was observed towards the end of the exercise period.

It is known that the glycogen depots of the body are limited (13) and consequently there is a subsequent need for an increased fat mobilization during prolonged severe exercise This is supported by the fact that fat-mobilizing hormones like HGH does not rise when glucose is given during exercise and utilized as a fuel (17) In the present investigation serum FFA was found to increase only slightly during the exercise period However after cessation of work the serum FFA showed a rapid and pronounced increase. The FFA levels were still above the resting values after 60 min of recovery These results from studies on pre-pubertal boys are substantially in agreement with the findings of Pruett (28) studying adult subjects.

However the factors which are responsible for the observed increase in FFA cannot be elucidated from the present investigation. Studies by Trygstad & Foss (35) ha e shown that increased HGH levels have a long lasting adipokinetic effect. It has been suggested that other hormones (i.e. epinephrine) also stimulate the release of FFA (11) and recent studies by Häggendal *et al* (9) have shown that the concentration of nor-epinephrine in blood is increased during exercise However the effect of nor-epinephrine is known to be short lived, and consequently only exerting an effect during the exercise period. In the present study only a small and insign ficant increase of FFA was found during exercise indicating that the work stress was not large enough to produce any pronounced FFA release The results of this and other studies (28) indicate that the mobilization of FFA is regulated by more than one factor It is reasonable to suggest that HGH might be one of the factors responsible for the FFA mobilization in the recovery period. To further evaluate the connection between HGH secretion and FFA mobilization simultaneous measurement of glycerol should be added

Exercise is also known to elicit changes in blood glucose and plasma insulin levels (26, 27). Prolonged exercise of moderate to heavy intensity (50—70 % of the maximal oxygen uptake) produces a significant decrease in blood glucose and plasma insulin concentrations. Prolonged severe exercise (75—80 % of maximal oxygen uptake) elicits little or no fall in blood glucose concentrations, but work at 85—90 % of maximal oxygen uptake which lasts for 10 minutes or more has been found to produce a small but significant increase in circulating glucose concentrations (27). Intermittant maximal exercise of short duration increases the blood sugar level by more than 100 % with a corresponding increase in plasma IRI (15). Thus it seems that the blood glucose response is dependent both on the intensity and the duration of the work.

In the 1969 study no significant increase was found in the plasma glucose concentration before and after work, while the 1970 study revealed a 12 % increase. The explanation for this might be that the relative work load was on an average approximately 5 % higher in the 1970 study indicating that exercise on work loads above 70 % of the maximal oxygen uptake in children induces a stress which acts on the glucose releasing mechanisms. In fact, the increase in plasma glucose concentration was found to be 26, 21 and 32 % in the 3 subjects working on 75 % or more of their maximal oxygen uptake. However the increase in plasma glucose concentrations was not accompanied by a corresponding increase in the plasma IRI. On the contrary plasma IRI decreased to approximately 80 % and 50 % of the pre-exercise values in the 1969 and 1970 studies, respectively indicating that the normal glucose/insulin relationship is altered during exercise. The results also indicate that this alteration is greater at higher relative work loads.

An enchanced glucose utilization during exercise has been well documented in numerous studies on both animals and man. However the nature of the mechanisms which facilitate cellular transport and oxidation of glucose has remained obscure. Nikkilä *et al.* (24) showed that moderate muscular exercise of short duration did not influence either insulin secretion rate, plasma insulin level or insulin utilization in normal adult men. During prolonged exercise various authors have found a slight fall in insulin levels (6, 21, 29) while Pruett (27) in young adult men found a fall to approximately 60 % of the pre-exercise level, which is substantially in agreement with the result of the present study.

It seems therefore justified to conclude that the enchanced glucose utilization during exercise must be attributed to factors other than insulin. The nature of these mechanisms is still unknown and subject to speculation.

SUMMARY

23 pre-pubertal boys were studied for three consecutive years from the time they were 10.5 years old (mean age). They ran on a motor driven treadmill for 60 min at a speed of appr. 70 % of the individual's VO_2 max.

Plasma glucose increased slowly during work and also during the first 5min of the recovery period. Plasma IRI decreased, the greatest fall was observed during the first 20 min of exercise. The HGH response was brisk and long lasting with a 7—8 fold increase during work, and a gradual fall after work stop.

The FFA response was insignificant during work, but a rapid increase ocurred during the first 5 min of the recovery period. This was followed by a steady fall during the next 25 min and then levelling off. The values 60 min after work stop were still well above the initial level.

The study indicates that HGH might be one of the factors responsible for the FFA mobilization [in] the recovery period. The blood glucose response was dependent both on the intensity and the duration of the work. The normal glucose/insulin relationship was altered indicating that the enhanced glucose utilization during exercise must be attributed to factors other than insulin.

REFERENCES

1. Bang, O. The lactate content of the blood during and after muscular exercise in man. *Skand. Arch. Physiol.* 74 Suppl. 10, 1936.

2. Blackard, W G and Heldingspelder, S. A. Adrenergic receptor control mechanism for growth hormone secretion. *J Cli I st,* 47 1407 1968
3. Carlsten, A., Hallgren, B Jagenburg, R Svanborg, A., and Werkö, L. Arterial concentrations of free fatty acids and free amino acids in healthy human individuals at rest and at different work loads. *Scand J Clin Lab I est* 14 185 1962.
4. Christensen, E. H., and Hansen, O Untersuchungen über die Verbrennungsvorgänge bei langdauernder schwer Muskelarbeit. *Skand Ar h Phy iol* 81 152, 1939
5. Christensen, E. H., and Hansen, O Arbeitsfähigkeit und Ernährung.*Skand Arch Physiol* 81 160, 1939
6. Cochran, B. Jr Marbach, E. B., Poucher R., Steinberg, T and Gwinup, G., Effect of acute muscular exercise on serum immunoreacti e insulin concentration. *Diabet* 15 838, 1966.
7. Greenwood, F C., Hunter W M., and Marrian, V Growth hormone levels in children and adolescents. *Brit m d J* 25: 1964, I.
8. Greenwood, F G., and Landon, J Growth hormone secretion in response to stress in man. *Na (Lond)* 210: 540, 1966.
9. Häggendal, J L., Hartley L H and Saltin, B. Arterial noradrenaline concentration during exercise in relation to the relati e work level. *Scand J Cli Lab I vest* 26 337 1970.
10. Hales, C. N., and Randle, P J Immunoassay of insulin with insulinantibody precipate. *Biochem J* 88. 137 1963.
11. Havel, R. J and Goldfien, A. The role of the sympathetic nervous system in the metabolism of free fatty acids. *J Lip Res,* 1 102, 1959
12. Havel, R. J Carlson, L. A., Ekelund, L.-G and Holmgren, A. Turnover rate and oxidation of different free fatty acids in man during exercise *J Appl Physiol,* 19 613, 1964.
13. Hermansen, L., Hultman, E and Saltin, B Muscle glycogen during prolonged severe exercise. *Acta Physiol Scand* 71 129 1967
14. Hermansen, L., and Saltin, B Oxygen ptake during maximal treadmill and bicycle exercise. *J Appl Physiol* 26, 31 1969
15. Hermansen, L Pruett,E D R Osnes J B and Giere, F A.. Blood glucose and plasma insulin in response to maximal exercise and glucose infusion *J Appl Physiol,* 29 13, 1970
16. Hultman, E.. Rapid specific method for determination of aldosaccharides in body fluids *Nature* 183. 108, 1959
17. Hunter, W M., and Greenwood, F C Studies on the secretion of human pituitary growth hormone. *Brit Med J* 1 804, 1965
18. Hunter, W M., Fonseka, C. C., and Passmore, R.. The role of growth hormone in the mobilization of fuel for muscular exercise. *Quart J Exp Physiol* 50: 106, 1965
19. Hunter W M., Friend, J A. R., and Strong, J A.. The diurnal pattern of plasma growth hormone concentration in adults. *J Endocr n* 34, 139 1966.
20. Hunter W M., and Rigal, W M.. The diurnal pattern of plasma growth hormone concentration in children and adolescents. *J Endocri* 34 147 1966.
21. Hunter W M and Sukkar M. Y.. Changes in plasma insulin levels during muscular exercise. *P oc Physiol Soc* 23, Feb. 1968.
22. Lazarus, L., and Young, J D. Radioimmunoassay of serum growth hormone in acromegaly *Proc Aust Phy iol Soc* 6, 1966.
23. M rimee T J Lillicarp D A and Rabinowitz, D Effect of arginine on serum-le ls of human growth hormone *The Lanc t* 668, 1965 II.
24. N kkilä, E A Taskinen, M R Miettinen, T A., Pelkonen, R., and Poppius, H. Effect of muscular exercise on insulin secretion. *Diabet s,* 17 209 1968.
25. Norman, N., and Turter A. R.: Radioimmunoassay studies with human growth hormone and pituitary l pid mobilizing factor *Acta Endocrin,* 58. 318, 1968.
26. Pruett, E D R Glucose and insulin concentrations during prolonged work stress in men living on different diets. *J Appl Physiol* 28. 199 1970
27. Pruett, E D R Plasma insulin concentrations during prolonged work at near maximal oxygen uptake. *J Appl Physiol* 29 155 1970.
28. Pruett, E D R FFA mobilization during and after prolonged severe muscular work in men. *J Appl Physiol,* 29 809 1970.
29. Rasio, E Malaisse, W Franckson, J R. M., and Conard, V Serum insulin during acute muscular exercise in normal man. *Arch Int Pharmacodyn* 160 485 1966
30. Roth, J Glick, S M Yalow R. S and Berson, S A.. Secretion of human growth hormone: Physiological and experimental modification. *Metabolism* 12 577 1963
31. Roth, J Glick, S M Yalow R. S., and Berson, S A.. Hypoglycemia A potent stimulus to secretion of growth hormone. *Scienc* 140. 987 1963.
32. Stanescu, V Florea, V Ionescu, V Dumitrescu, E., and Stanescu, R. L proline loading test in growth disturbances. *Hel Paed Acta,* 23 147 1968.
33. Sutton, J R., Young, J D Lazarus, L., Hickie, J B and Maksvytis, J The hormonal response to physical exercise *Aust A Med* 18. 84, 1969

34. Trout, D. L., Harvey Estes, E. Jr. and Friedberg, S. J. Titration of free fatty acids of plasma. A study of current methods and a new modification. *J. Lip. Res.* *1*: 199, 1960.
35. Trygstad, O. and Foss, L. The lipid-mobilizing effect of some pituitary gland preparations. IV. Subdivision of human growth hormone preparation into a somatotrophic and an adipokinetic hyperglycemic agent. *Acta Endocr.* *58*: 295, 1968.
36. von Euler, U. S. and Hellner, S. Excretion of noradrenaline and adrenaline in muscular work. *Acta Physiol. Scand.* *26*: 183, 1952.
Key words: Prolonged exercise, immunoreactive human growth hormone, plasma free fatty acids, plasma glucose, plasma immunoreactive insulin.
(S.O.) Pediatric Research Institute
University Hospital, Rikshospitalet
Oslo, Norway

Acta Paediat Scand Suppl 217 1971

MUSCLE METABOLITES DURING EXERCISE IN PUBERTAL BOYS

BENGT O ERIKSSON JAN KARLSSON and BENGT SALTIN

From the Department of Physiology Gymnastik- och Idrottshögskolan and the Department of Pediatrics Karolinska Institutet St Göran's Children Hospital Stockholm Sweden

Aerobic power is the same or greather in children expressed per kg body weight than in adults (1) On the other hand, children s anaerobic capacity appears to be lower at least to judge from data on blood lactate concentration after exhaustive exercise. The reason for this has been the subject of discussion but no satisfactory explanation has yet been produced.

This study was performed in order to study this question further and to collect more information on metabolic responses in children during exercise. A more detailed presentation of the study can be found elsewhere (3)

METHODS AND PROCEDURE

A group of eight healthy 13-year old boys performed graded exercise on a bicycle ergometer (300, 600 and 900 kpm/min) lasting 6 min up to maximal exercise (900—1350 kpm/min) Their height, weight and moreover testicular size according to Buhr *et al* (2) were measured (Table 1) At each work level heart rate and oxygen uptake were determined during the last 1—2 min of exercise these determinations were also made continously for four of the subjects from the start of work. Muscle biopsies were taken from the lateral part of the quadriceps femoris at rest and immediately after the stop of each work load The muscle specimens were quickly frozen in liquid nitrogen and subsequently analyzed for glycogen glucose-6-phosphate (G-6-P) lactate, adenosine triphosphate (ATP) and creatine phosfate (CP) as described by Karlsson (4) As subjects were sitting on the bicycle when biopsies were taken after each work load, all muscle samples could be frozen within 3—5 seconds after cessation of exercise. Blood lactate were taken at the same time as muscle biopsies and analyzed with an enzymatic method (6)

Table 1 *Some physical data of the subjects*

No. of subj.	Age yrs	Height cm	Weight kg	Testicular volume index
8	13 6	162	50 6	11.0
	13.1—14 8	153—173	39 7—63 9	5 3—15.8

RESULTS

Mean oxygen uptake during maximal work when the biopsies were taken was 2 57 l/min which is comparable to 2 58 l/min, the highest value observed in these boys. The mean maximal heart rate was 195 beats/min in the present study which was 6 beats/min lower ($p < 0.05$) than the highest observed with maximal exercise in the present subjects. Even the maximal blood lactate concentration was in the same range when compared to the highest observed value A mean maximal oxygen uptake value of 50 ml/kg/min may be regarded as representative for this age group.

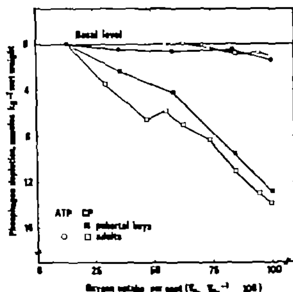


Fig. 1 Mean values for phosphagen depletion during exercise in pubertal boys compared to adult males. Oxygen uptake is given as per cent of maximal oxygen uptake.

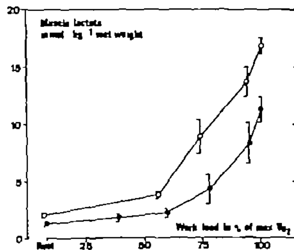


Fig. 3. Muscle lactate concentration in pubertal boys (filled symbols) compared to adult males (unfilled symbols) (Means ±S.E.) at different workloads expressed as per cent of the maximal oxygen uptake.

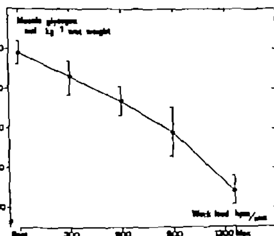


Fig. 2. Mean muscle glycogen concentration in mmoles/kg wet weight with ±S.E. in pubertal boys at different work loads to maximal level.

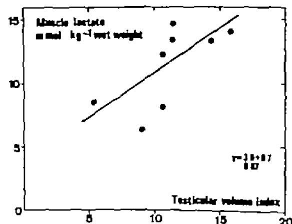


Fig. 4. Individual values for maximal muscle lactate concentration obtained at maximal exercise compared to testicular volume index.

Metabolic data are presented in Fig. 1—5. ATP concentration declined from a mean value of 5.0 at rest to 3.9 mmoles/kg wet muscle. This significant decrease was only seen with exhaustive exercise (Fig. 1). A more gradual and definite decrease was observed for CP (Fig. 1). The mean value at rest was 17.0 mmoles/kg wet muscle, an almost linear reduction was observed until exhaustion at which time the mean concentration was 4.9 mmoles/kg wet muscle. The muscle glycogen level at rest was 69 mmoles glucose units/kg wet muscle and a reduction was observed with each work period (Fig. 2). The mean value was 34 mmoles/kg after the last exercise period.

The muscle lactate concentration with subjects at rest was 1.3 mmoles/kg wet muscle and it increased very little at the lowest work loads (Fig.

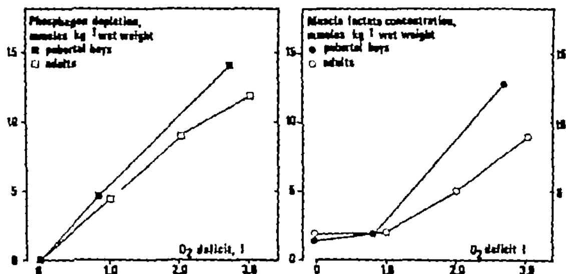


Fig. 5 Phosphagen depletion and muscle lactate concentration in pubertal boys and adult males compared to O_2 deficit.

3) With work loads demanded more than 60 per cent of the maximal oxygen uptake a more rapid increase was observed but mean maximal concentration was only 11.3 mmoles/kg

Blood lactate concentration reflected muscle lactate concentration. Rather striking individual variations in muscle lactate concentration were observed in the group. This was most pronounced at the exhaustive work load at which concentration ranged from 6.3 to 14.6 mmoles/kg wet muscle. As the boys differed in respect to pubertal development, the observed maximal muscular lactate level was related to each boy's degree of maturation, interpreted on the basis of the testicular volume index (2). It was then found that the boys with the highest muscle lactate values also had the greatest testicular volumes (Fig. 4)

DISCUSSION

The reduction in phosphagen stores with exercise was very similar in the present groups of boys as compared to adult males (4). On the other hand, very striking differences were observed for muscle and blood lactate concentrations when the boys were compared to adult males. Blood lactate concentrations during submaximal and maximal exercise in the present material comprising 13-year old boys were in very good agreement, however with results obtained by Astrand (1) in the same age group. It seems most likely that the reason for the lower blood lactate concentration in young subjects after exercise is due to a lower production of lactate. In adults there is good correlation between oxygen deficit at start of heavy exercise and the lactate concentration (5). The oxygen deficit was determined for four of the present subjects. The results indicate that there is also good correlation in these boys between oxygen deficit and muscle lactate concentration (Fig. 5). The question then is why boys are unable to attain higher oxygen deficits. The almost significant correlation between maximal muscle lactate attained and the testicular volume index suggests that the subject's sexual maturation exerted an influence on the lactate production. However it is far from clear which factors are brought into play in this respect.

SUMMARY

After heavy exercise in children a low blood lactate concentration is a common finding. In the present study it is shown that the lactate concentration in exercising muscles at maximal work also

is low mean values reaching only 11 (6—15) mmoles/kg. The accumulation of lactate was well related to the oxygen deficit at onset of work. Any explanation to the low marginal oxygen deficits and muscle lactate concentrations found in children cannot be given. The observed relationship between maximal muscle lactate concentration and the testicular volume index suggest that sexual maturation has a role.

ACKNOWLEDGEMENT

This study was supported by the Swedish Medical Research Council Project No 14X 2203

(B E) Barnkliniken, St Görans sjukhus,
Box 125 00, S-112 81 Stockholm, Sweden

Key words. Pubertal boys, testicular volume index, maximal oxygen uptake, blood lactate, muscle biopsies, muscle lactate, glycogen, ATP and CP phosphogen depletion, oxygen deficit.

REFERENCES

1 Astrand, P-O *Experimental studies of physical working capacity in relation to age and sex* Munksgaard, Copenhagen, 1952.

2. Burr L, Sizonenko, P Kaplan, S. and Grumbach. M. Hormonal changes in puberty 1. Correlation of serum luteinizing hormone and follicle stimulating hormone with stages of puberty testicular size and bone age in normal boys. *Pediat Res* 4 23 1970.

3. Eriksson, B. O Karlsson, J. and Saltin, B Muscle metabolites during exercise in 13 year-old boys. *J Appl Physiol* To be published.

4. Karlsson, J Lactate and phosphagen concentrations in working muscle of man *Acta Phys Scand*, suppl. 358, 1971

5 Karlsson, J and Saltin, B Lactate, ATP and CP in working muscles during exhaustive exercise in man, *J Appl Physiol* 29. 598, 1970.

6. Scholz, R., Schmitz, H., Bücher T and Lampe, J-O.: Über die Wirkung von Nystatin auf Bäckerhefe. *Biochem Z.* 331 71 1959

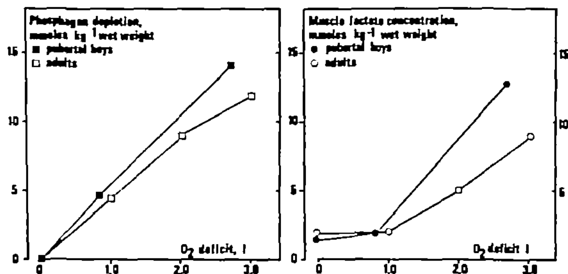


Fig. 3. Phosphagen depletion and muscle lactate concentration in pubertal boys and adult males compared to O_2 deficit.

3) With work loads demanded more than 60 per cent of the maximal oxygen uptake a more rapid increase was observed but mean maximal concentration was only 11.3 mmoles/kg.

Blood lactate concentration reflected muscle lactate concentration. Rather striking individual variations in muscle lactate concentration were observed in the group. This was most pronounced at the exhaustive work load at which concentration ranged from 6.3 to 14.6 mmoles/kg wet muscle. As the boys differed in respect to pubertal development, the observed maximal muscular lactate level was related to each boy's degree of maturation, interpreted on the basis of the testicular volume index (2). It was then found that the boys with the highest muscle lactate values also had the greatest testicular volumes (Fig. 4).

DISCUSSION

The reduction in phosphagen stores with exercise was very similar in the present groups of boys as compared to adult males (4). On the other hand, very striking differences were observed for muscle and blood lactate concentrations when the boys were compared to adult males. Blood lactate concentrations during submaximal and maximal exercise in the present material comprising 13-year old boys were in very good agreement, however with results obtained by Astrand (1) in the same age group. It seems most likely that the reason for the lower blood lactate concentration in young subjects after exercise is due to a lower production of lactate. In adults there is good correlation between oxygen deficit at start of heavy exercise and the lactate concentration (5). The oxygen deficit was determined for four of the present subjects. The results indicate that there is also good correlation in these boys between oxygen deficit and muscle lactate concentration (Fig. 5). The question then is why boys are unable to attain higher oxygen deficits. The almost significant correlation between maximal muscle lactate attained and the testicular volume index suggests that the subject's sexual maturation exerted an influence on the lactate production. However it is far from clear which factors are brought into play in this respect.

SUMMARY

After heavy exercise in children a low blood lactate concentration is a common finding. In the present study it is shown that the lactate concentration in exercising muscles at maximal work also

is low mean values reaching only 11 (6—15) mmoles/kg. The accumulation of lactate was well related to the oxygen deficit at onset of work. Any explanation to the low marginal oxygen deficits and muscle lactate concentrations found in children cannot be given. The observed relationship between maximal muscle lactate concentration and the testicular volume index suggest that sexual maturation has a role.

ACKNOWLEDGEMENT

This study was supported by the Swedish Medical Research Council Project No 14X 2203

(B E.) Barnkliniken, St Görans sjukhus,
Box 125 00, S-112 81 Stockholm, Sweden

Key words. Pubertal boys, testicular volume index, maximal oxygen uptake, blood lactate, muscle biopsies, muscle lactate, glycogen, ATP and CP phosphogen depletion, oxygen deficit.

REFERENCES

1 Astrand, P -O *Experimental studies of physical working capacity in relation to age and sex.* Munksgaard, Copenhagen, 1952.

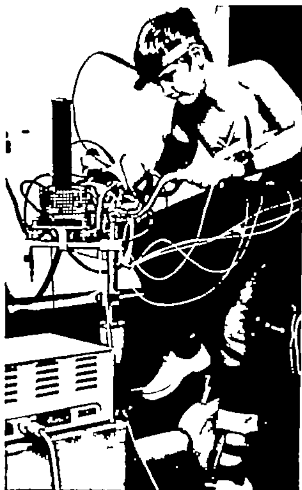
2. Burr I Sizonenko, P Kaplan, S and Grumbach. M. Hormonal changes in puberty 1 Correlation of serum luteinizing hormone and follicle stimulating hormone with stages of puberty testicular size and bone age in normal boys. *Pediat Res* 4. 25, 1970

3 Eriksson, B O Karlsson, J and Saltin, B Muscle metabolites during exercise in 13 year-old boys. *J Appl Physiol* To be published.

4. Karlsson, J Lactate and phosphagen concentrations in working muscle of man *Acta Phys Scand*, suppl 358, 1971

5 Karlsson, J and Saltin, B Lactate, ATP and CP in working muscles during exhaustive exercise in man, *J appl Physiol* 29. 598 1970

6 Scholz, R Schmitz, H Bücher T and Lampe, J.-O Über die Wirkung von Nystatin auf Bäckerhefe. *Biochem Z* 331 71 1959







List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics.* Lisbon, 1962. Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar, Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic study. Sw. kr. 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr 25.— 1964
157 Brante, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Pediatric Congress.* Stockholm, 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Peltonen, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 30.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 15.— 1966
[illegible] Torben, Leukaemia in Infancy and Childhood. A Material of 370 Danish Cases. Sw. kr. 30.— 1966
[illegible]berg, W. Focal Spike Discharges in Children. Longitudinal Study. Sw. kr. 25.— 1966
[illegible] Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
Bellman, Margaret, Studies on Encopresis. Sw. kr. 30.— 1966
Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr 20.— 1966
172. *Festschrift in Memory of Constantin Chaeramis.* Sw. kr. 15.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to hemodynamic function. Sw. kr. 25.— 1967
175. Hänninen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen. 1967. Sw. kr. 35.— 1967
178. Sjögren, Ivan, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr 25.— 1967
180. Andersen, Hans Jürgen, Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Gösta, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Elsa, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter, et al., The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr 30.— 1968
188 Meeuwisse, Gunnar W., and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Kolräka, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kumento, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw kr. 20.— 1969
197 Renola, Reino, Postoperative Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw kr. 30.— 1969
200. Sanjur, Diva M., Cravioto, Joaquin, Rosales, Lydia and van Veen, André Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette E., Hartwell, Phyllis, Balis, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr, L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw kr 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw kr 35.— 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw kr 35.— 1970
210. Rosberg, Georg, Parental Attitudes to Pediatric Hospital Admissions. Sw. kr. 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Hakulinen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971
214. Samuelson, Gösta, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 25.— 1971
215. Bergsten, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr 25.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217 *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium.* Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. Sw. kr. 35.— 1971

Price Swed. kr 35 —

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 216 1971

CRY ANALYSES OF SYMPTOMLESS *LOW BIRTH WEIGHT* NEONATES AND OF ASPHYXIATED NEWBORN INFANTS

BY KATARINA MICHELSSON

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

CRY ANALYSES OF SYMPTOMLESS LOW BIRTH WEIGHT NEONATES AND OF ASPHYXIATED NEWBORN INFANTS

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENTUM 216

Department of Pediatrics University of Oulu, Finland
Wenner-Gren Medical Research Laboratory Norrtull Hospital, Stockholm Sweden

CRY ANALYSES OF SYMPTOMLESS LOW BIRTH WEIGHT NEONATES AND OF ASPHYXIATED NEWBORN INFANTS

by

Katarina Michelsson

HELSINKI 1971

But what am I?
An infant crying in the night
An infant crying for the light.
And with no language but a cry

Alfred Lord Tennyson
1809—1892

CONTENTS

INTRODUCTION 10

REVIEW OF THE LITERATURE 11

A. ASPHYXIA IN INFANTS 11

B. CRYING IN INFANTS 12

1. Auditory investigations 12

2. Audiovisual investigations 12

PURPOSE OF THE STUDY 14

SERIES OF NEONATES 15

A. *CRITERIA OF THE DIAGNOSIS GROUPS* 15

B. GROUP I LOW BIRTH WEIGHT NEONATES 15

C. GROUP II ASPHYXIATED NEONATES 16

1. Neonates with dominating peripheral respiratory disturbances 16

2. Neonates with dominating respiratory center failure 16

D. FOLLOW UP OF THE INFANTS 18

METHODS 19

A. RECORDING OF THE CRIES 19

B. ACOUSTIC MEASUREMENTS 19

C. CHARACTERISTICS OF CRY-SOUND 19

RESULTS 22

A. *GROUP I LOW BIRTH WEIGHT NEONATES* 22

1. Small-for-date neonates 22

2. Premature infants 22

3. The typical cry-signal of symptomless newborn infants 24

B. GROUP II ASPHYXIATED NEONATES 26

1. Neonates with dominating peripheral respiratory difficulties 30

2. Neonates with dominating respiratory center failure 30

3. The characteristics of abnormal cry-signals in asphyxiated neonates 33

DISCUSSION AND CONCLUSIONS 34

A. SIGNIFICANCE OF DIFFERENT CRY-CHARACTERISTICS 34

B. CHARACTERISTICS OF CRY IN LOW BIRTH WEIGHT NEONATES 34

C. SIGNIFICANCE OF ABNORMAL CRY IN ASPHYXIATED NEONATES 35

D. CLINICAL USEFULNESS OF CRY-STUDIES 36

SUMMARY 39

ACKNOWLEDGEMENTS 41

REFERENCES 42

INTRODUCTION

Many factors causing neonatal morbidity and mortality arise just before, during or immediately after delivery and thus often cause a delayed onset of adequate respiration. The increased possibilities of analyzing the clinical state and of applying treatment have created a demand for new methods to clarify the exact cause of neonatal asphyxia.

The present investigation especially aims to study the crying of newborn infants with asphyxia, by evaluating whether the results of the cry analyses of these infants differ from those of healthy neonates, and if the analyses could give any information regarding the cause of neonatal asphyxia.

The research group, to which the author belonged, collected the cries of healthy infants in 1962 and 1963. It was already at that time suspected that there might be differences in the crying of asphyxiated newborn infants. Now as the base-line of a normal infant's cry is established (115) it has been possible to continue the study with the method used.

However there are no data available concerning the crying of low birth weight infants born after uncomplicated deliveries. Therefore, the cry analysis of this group is also included here.

REVIEW OF THE LITERATURE

A. ASPHYXIA IN INFANTS

Neonatal asphyxia, which can be defined as "oxygen deficiency in vitally important organs" (54) may occur before and/or during delivery and/ r after birth (105) The longer asphyxia exists, the more likely are death or permanent damage to occur (16, 22, 23, 102, 105)

As causes of neonatal asphyxia Towell (105) differentiates between maternal, placental and foetal o neonatal factors.

Foetal distress during pregnancy or labour is frequently associated with changes in foetal heart rate, presence of meconium in amniotic fluid, and changes in acid-base balance in foetal blood samples (62, 81 102, 105) Neonatal asphyxia is often a continuation of intrapartum anoxia, which may initiat gasping in utero with aspiration of amniotic fluid and meconium (105) After birth the clinical evaluation of the infant s condition using the Apgar scoring system (6, 7) has shown that the five-minute score has a stronger correlation with infant mortality and morbidity than the one-minut score (22, 23)

In the Textbook of Pediatrics (81) the neonatal factors in asphyxia are separated into two groups, those caused by *peripheral respiratory difficulties* of pulmonary or cardiovascular origin, and those caused by *central nervous system failure* with depression of the respiratory center

The diagnoses of peripheral respiratory disturbances are often based on the symptoms of rapid respiratory rate, cyanosis, intercostal and xiphoid retractions, and expiratory grunting (81, 99).

The diagnosis of intracranial disease in neonatal asphyxia has often been clinically established from one or more of the symptoms of convulsions, rigidity respiratory disorders, unconsciousness, or refusal to suck (19 21, 39 40 41, 54, 81, 104)

Joppich and Schulte, 1968 (54) and Thorn, 1969 (104) have reviewed previous investigations of clinical symptoms of asphyxia and their prognostic significance.

Joppich and Schulte, (54) divided the asphyxiated infants into those with hyperexcitability caused by a relatively mild hypoxia, those with symptoms of apathy and lethargy caused by a somewhat more severe hypoxia and those with muscular rigidity focal neurological symptoms, or extreme hypotonia, these symptoms being seen in the most severely asphyxiated infants.

In her study comparing the features of infants dying in the neonatal period from pulmonary atelectasis r intracranial lesions, Thorn, 1969 (104) found that convulsions, tremor rigidity and irritability occurred exclusively in those with brain damage. Also cyanotic attacks after the first day of life were found in brain-damaged infants only However the absence of these signs did not exclude the diagnosis of intracranial haemorrhage or oedema.

A clinical distinction between pulmonary disorders and intracranial lesions is not always clear and the tw conditions may coexist (105). However severe pre- or perinatal anoxia always produces a central nervous type of respiratory failure (102, 105)

B. CRYING IN INFANTS

1 *Auditory investigations*

Crying may begin before birth (18, 20, 60, 92).

After birth crying is said to have physiological usefulness in the early days of neonatal adjustment (14, 71, 122), as improving pulmonary capacity in the first days of life (71) or being a defence mechanism to increase body temperature (122).

Many auditory investigations of infant vocalization are observations of when, why and how much the baby cries (2, 3, 4, 5, 14, 15, 42, 96, 125). Some correlation has been found in the crying activity compared to Apgar scoring (59) or later intelligence scoring (17, 58).

Sherman (103), Miller (79) and van Riper (98) are often quoted as stating that neonatal crying has little intent or meaning. However many other authors believe there are differences, varying with stimuli, in infant vocalization (1, 10, 31, 42, 53, 77, 90). Also the crying of infants with many diseases, such as kernicterus (55), Down's syndrome (26, 93), cretinism (55) and the cri du chat syndrome (43) is said to have certain characteristics. The crying in diseases of intracranial [illegible] n has been characterized as "high-pitched" [illegible]) or "shrill" (102, 108).

[illegible]e graphophon was the first apparatus used [illegible] Flatau and Gutzmann in 1906 for the analyses of infant vocalization (29). They studied the crying of 30 neonates and found a fundamental frequency of 440 Hz, and also noted a more high-pitched phonation in 3 infants.

Lewis, in 1936 (65), pioneered in making notes on infant utterances using the International Phonetic Alphabet, later used in studies of infant vocalization also b[illegible] other[illegible] (25, 44, 45, 46, 47, 48, 49, 50, 51).

From gramop[illegible]r[illegible]rds Fairbanks, 1942 (24) studied th[illegible] freq[illegible]haracteristics of infant "hunger w[illegible]l[illegible]n[illegible] of [illegible] er a period of 9 months. He [illegible] fundamental frequency of 373 Hz d[illegible]ring th[illegible] f[illegible]rst m[illegible]nth and 556 Hz during the entir[illegible] 9 month p[illegible]

Gramophone rec[illegible] 3[illegible] 50[illegible]a[illegible]pe recording (89) ha[illegible]e[illegible]n made to ill[illegible]strate the sequences in speech development. Gramophone records are also available in appendix with the monographs edited by Lind, 1965 (66), and Wasz Höckert 1968 (115). A recording entitled "Sound Diagnosis" was produced in 1970 (123).

Wasz Höckert et al., 1964 (117) and Michelsson et al., 1965 (78) have found from tape recordings that hunger, pain, pleasure and birth cries can be identified auditorily. Valanne et al., 1967 (107), found that mothers can recognize the vocalization of their own infant, as also stated by Formby in 1967 (30). Partanen et al, 1967 (91) demonstrated that the pain cries of healthy infants could be differentiated from the crying of sick ones.

Massengill et al., 1966 (75) and 1968 (76) found that speech clinicians were not able to recognize the grade of nasality (75) or the type of crying (76) of cleft-palate infants.

Ostwald et al., 1962 (85), analysed with a half octave-band analyser the crying of 16 pairs of twins and stated that factors other than heredity determine similarities and differences between the cries of twin-partners. Ostwald, 1963 (84) located in half-octave-band analyses the fundamental tone of normal neonate crying between 435—600 Hz.

Gleiss and Höhn, 1968 (32) found in the cry analyses of 50 prematures, 39 healthy and 11 with pulmonary disorders, a mean latency of 2.1 seconds, and that the latency period shortens with repeated stimulation. The mean value of the duration of the phonations was 1.5 seconds. A second latency occurred more often in abnormal infants, who also cried for shorter periods.

2. *Audiovisual investigations*

Studies with amplitude recorders

The volume-unit graph was used by Fisichelli et al., 1961 (28) and 1963 (27), and Karelitz and Fisichelli, 1962 (57). They found that infants with diffuse brain damage require a greater stimulus to produce one minute crying (57) and that the mean latency period between pain stimulus and onset of crying was longer for abnormal infants,

2.6 seconds compared to 1.6 seconds in healthy infants (27)

Minnigerode, 1963 (80), studied, with a 6-channel amplitude recorder high-pitched parts in infant crying, but found only 6 cases in 100 infants from 10 days to 12 months of age.

A direct writing oscillograph was used by Lind et al., 1966 (69), in comparing the vocal responses of five brain-damaged babies with 180 healthy controls, and in later duration measurements of crying, in connection with spectrographic investigations (61, 67 110, 114, 115)

Sound spectrographic investigations

The sound spectrograph was presented under the name "Visible Speech in 1947 by Potter et al. (94), and used in phonetic connections for the first time by Joos in 1948 (52) In Finland, sound spectrography has scientifically been used on adults by laryngologists (63, 88) and in phonocardiologic studies of children (64)

The first investigation of infant vocalization with the sound spectrograph was made by Lynip in 1955 (73) He analysed the vocalization of one infant from birth to the age of 56 weeks using phonetic symbols as also used by others in spectrographic analyses of prelanguage utterances (100, 101, 124) Lynip found a fundamental frequency of 360—420 Hz in the first non-crying utterances.

In 1961, in Helsinki, a research group was organized to study infant vocalization. The first preliminary report was published in 1962 (120) by Wasz Höckert, Vuorenkoski, Valanne and Michelsson. In 1963 (119) and 1964 (116) the study group showed that hunger pain, birth and pleasure signals can be differentiated.

From the aspect of newborn physiology in 1965 a research group in Stockholm, headed by Lind and, using previous cineradiographic methods (11, 12) published their monograph based on sonograms of 30 newborn infants in connection with cineradiographic investigations (66). They referred to three acoustic sorts of cry as phonation (basic cry), dysphonation (turbulence) and hyperphonation (shift)

In 1963 the research group headed by Wasz Höckert joined the Lind-group and a number of studies have been published since (36, 61 67 68, 69 70, 107 109 110, 111, 112, 113, 114 115, 118, 121)

A monograph concerning the analyses of birth, pain, hunger and pleasure signals in healthy full-term newborn and young infants was published in 1968 (115). The mean value of minimum and maximum pitch in pain-stimulated crying was 410—380 Hz and 650—680 Hz, respectively The monograph also included results of human identification of cry-signals, and spectrographic analyses of some abnormal infants crying.

Sound spectrography was further used by Ostwald et al. (85) who, in connection with half octave-band analyses, made spectrograms of two pair of twins, and in 1968 (87) analysed the cry of 13 infants classified, on the basis of clinical data, as normal, impaired or abnormal. They found that the signals with the highest value of fundamental frequency all occurred in impaired or abnormal infants.

In 1964 Ringel and Kluppel (97) reported normative cry data on 10 infants. They found a fundamental frequency of 413.13 Hz, a duration of 1 47 seconds and a sound pressure of 82.13 db 12 inches from mouth. Spectrographic analyses have further been made on infants with "Cat-cry" syndrome (9 3, 72), Down s syndrome (33, 82) and an infant with 13—15 trisomy (86) The crying in infants with "Cat-cry" syndrome had a more high pitched, and those with Down s syndrome or 13—15 trisomy generally low fundamental frequency pattern.

PURPOSE OF THE STUDY

The purpose of the present investigation was to study the pain induced crying of newborn asphyxiated infants, and of low birth weight neonates born after uncomplicated deliveries.

The research was designed

I. To obtain normative cry data of newborn low birth weight infants without pathological symptoms.

II To determine the possible differences between the crying of symptomless neonates and of those with asphyxia at and/or immediately after birth.

III To look for possible variations in the cries of asphyxiated newborn infants.

SERIES OF NEONATES

The present study comprises *310 neonates* of 0—10 days of age, whose pain induced crying was studied by sound spectrographic analyzing methods. The cries of the infants were collected in 1966 and 1967 at the Institute of Midwifery Helsinki (270 infants) or at the Department of Pediatrics, University of Oulu (40 infants). In addition, the author had access to data on the crying of *50 healthy full-term neonates* of 0—10 days of age, published in detail elsewhere (115) of which a large part were originally recorded by the author at the Institute of Midwifery in 1962 and 1963. These data have been used as refer ence material.

Information about pregnancies and deliveries was available from record of the Institute of Midwifery Helsinki or the Department of Obstetrics, University of Oulu.

A. CRITERIA OF THE DIAGNOSIS GROUPS

The 310 neonates were divided according to clini cal data into two main groups, as shown in Table I.

I. The *first group* comprised *105 low birth weight* infants (≤ 2500 g) born after uncomplicated deliveries and with no signs of distress bef re, during or after delivery

II. The *second group* consisted of *205 asphyxiated* newborn infants who immediately after birth suffered from respiratory failure or distress. They were di ided into two different gro ps (1) those considered suffering mainly from *peripheral respiratory difficulties* (80 neonates), and (2) those with asphyxia resulting mainly from *failure f the respiratory center* (125 neonates)

TABLE 1 *The number of newborn infants in the d fferent groups*

Group	No.
I. NEONATES WITH LOW BIRTH WEIGHT	
small-for-date	30
premature	7[illegible]
total	105
II. NEONATES WITH RESPIRATORY DISTRESS OR FAILURE	
dominating peripheral respiratory difficulties	80
dominating central respiratory failure	125
total	205
TOTAL NUMBER OF NEONATES	310

B. GROUP I LOW BIRTH WEIGHT NEONATES

Of the low birth weight neonates 30 were small-f r-date (born after 38—40 weeks of gestation) and 75 were premature (born ≤ 37 weeks of gestation).

The birth weights aried in the small-for-date group between 1700 and 2500 grams and in the premature group between 740 and 2480 grams. Eleven of the infants were born by breech pre sentation, the others by cephalic presentation. The Apgar scores were 8—10 at birth and 9—10 at 15 minutes of age. At the time of cry-recording there was n acidosis in blood samples of these neonates and Hb blood sugar and bilirubin values were within normal limits.

C. GROUP II ASPHYXIATED NEONATES

The asphyxiated neonates were, as mentioned earlier divided into two main groups, those with dominating signs of peripheral respiratory disturbances and those where signs of failure of the respiratory center were the most obvious.

1 Neonates with dominating peripheral respiratory disturbances

This group comprised 80 newborn infants, 40 full-term and 40 premature with birth weights varying between 1550 and 4820 grams.

The diagnosis of respiratory distress was regarded clinically to be verified if two or more of the following criteria were present persistent respiratory rate over 60 per minute, intercostal and sternal retractions, expiratory grunting, or cyanosis when breathing room air The occurrence of these symptoms is listed in Table 2, as are the Apgar scoring, the diagnosis from clinical examination and the grade of acidosis at the time of recording.

Two mothers had toxaemia and one diabetes during pregnancy No labour lasted over 24 hours. 3 deliveries the amniotic fluid was discoloured and in 9 there were changes in foetal heart rate. 8 babies were born by breech presentation, 4 were twin-partners. There were no other abnormal occurrences during the deliveries

Three of the infants in this group had tremor at 2—3 days of age and were hypotonic. One neonate with congenital heart disease had at the time of the tape recording, one day before death developed muscular rigidity No other obvious signs of neurological disturbances were observed in these infants.

2 Neonates with dominating respiratory center failure

This group included 125 neonates, 70 full-term and 55 premature, birth weights varying between 800 and 4800 grams.

All neonates in this group had an Apgar score of 1—7 at birth and 60 of them also had signs of intrauterine anoxia with changes in foetal heart rate and/or discoloured amniotic fluid Thirty eight deliveries lasted over 24 hours. The complications of pregnancy and delivery and the distribution of the Apgar scores are listed in Table 3. Two of the infants were born by caesarean section after a preliminary attempt to deliver by vacuum extraction.

TABLE 2. *The distribution of Apgar scores the clinical symptoms and diagnosis and number of deaths in infants with dominating peripheral respiratory distress*

		Apgar scoring at 1 minute			Apgar scoring at 15 minutes					clinical symptoms at time of cry analyses: breathing frequency over 60/min.									clinical diagnosis				deaths
	number of infants	1	3	4	1	3	4–6	7	10	1	2d	≥3d	cyanosis	retractions	expirat. grunting	pH < 7,25	pCO_2 > 60	BE < —10	IRDS or pulm. atelect.	pneumonia, aspir. or pneumothorax	pulm. sequestration	cong. heart anom.	
full-term	40		—	ℓ			1		59		14	26	19	24	21	17	9	4	12	20	1	7	4
premature	40		1	7		—			39		4	36	16	24	21	28	21	8	30	8		2	12
total	80		1	15		—	2		78		18	62	35	48	42	45	30	12	42	28	1	9	16

TABLE 3. *The occurrence of complications of pregnancy or delivery and the distribution of Apgar scores in infants with dominating central asphyxia*

	complications of pregnancy and delivery												Apgar scoring at					
													1 minute			15 minutes		
	number of infants	toxaemia	prolonged labour	discoloured amniotic fluid	changes in foetal heart rate	cord round the neck	premature separation of placenta	prolapse of the cord	breech or foot presentation	vacuum extraction	forceps	caesarean section	1–3	4–6	7–10	1–3	4–6	7–10
full-term	70	13	24	32	21	3	4	2	10	19	3	17	30	32	8	5	26	39
premature	55	10	14	19	12	2	3	1	5	1	—	9	12	34	9	4	14	37
total	125	23	38	1	33	7	7	3	15	20	3	26	42	66	17	9	40	6

TABLE 4. *The occurrence of clinical signs and the number of deaths in infants with dominating central asphyxia*

	clinical symptoms													deaths
	number of infants	convulsions	tremor	irritability	rigidity	opisthotonos	cyanotic attack	hypotonia	abnormal Moro response	abnormal grasping	bad sucking	frequent vomiting	liquor changes	pH < 7.20	
full term	70	9	9	13	16	7	10	20	13	14	10	12	7	7	3
premature	55	6	9	7	6	5	16	16	14	13	22	8	6	12	12
total	125	15	18	20	22	12	26	36	27	27	32	20	13	19	15

Table 4 shows the occurrence of clinical symptoms and number of deaths. Three of the infants had a respiratory rate above 60 per minute for the first day of life but no other signs of peripheral respiratory disturbances and the central type of asphyxia was dominant.

D. FOLLOW-UP OF THE INFANTS

All the infants listed above were *followed up and investigated at the age of 1½–3 years*. Regular check-ups were performed by pediatricians in Helsinki, either at well-baby clinics or Aurora City Hospital. The author has additionally investigated those infants considered in some respect abnormal. In Oulu the check-ups were made by the neonatological staff at the Department of Pediatrics, University of Oulu.

The autopsies were performed by M. Arko, M.D., pathologist at the Institute of Midwifery, Helsinki, or J. Hakosalo, M.D., from the Department of Pathology, University of Oulu.

Low-birth weight infants. Three infants with birth weights of 740, 1200 and 1240 grams died at the age of 2, 4 and 25 days respectively. No abnormalities except immaturity were seen at autopsy. One infant was found at follow up to have a congenital heart disease, not observed in the neonatal period. No obvious neurological abnormalities were found at follow up.

Sixteen infants with *peripheral respiratory distress* died in the neonatal period. At autopsy nine of these had pulmonary atelectasis and hyaline membranes 3 pulmonar haemorrhage and 3 congenital heart disease. One twin-premature with pneumothorax after birth was by control less developed than the healthy twin-pair. No other probable neurological abnormalities were found at follow up.

Fifteen infants with *central respiratory failure* died in the neonatal period, and all had central haemorrhages at autopsy. Twentyseven infants were neurologically abnormal at check up, 7 had cerebral palsy 8 slow mental development, 8 had convulsions 3 of these also mentally retarded. One manifested Lowes syndrome. At follow-up, 3 infants had chromosomal aberrations, one had a 13—15 trisomy and one an abnormal 5 th chromosome. One infant had Down's syndrome, this had not been definitely diagnosed in the neonatal period otherwise, these infants were excluded from the investigation.

METHODS

A. RECORDING OF THE CRIES

The recordings of the cry-signals were made in all symptomless low birth weight infants within the first 10 days of life, in the asphyxiated neonates within 3 days after birth.

All the cries were pain cries recorded after pinching the skin of the upper arm of the infant. The pinch lasted as long as it took to say the word "now" which word was recorded.

The recordings were made with recording speed of 19 cm/sec and with a transistorized tape recorder Uher Report 4000 S (Uher W rke, München) A dynamic microphone AKG D 58 was used and was held 5 cm abo the infant s mouth. Both the tape recorder and the microphone ha e a quite satisfactory quality in the range of 50—8000 Hz.

B. ACOUSTIC MEASUREMENTS

The latency period, the duration of the phonation and th second pause were measured with a direct writing oscillograph, the Mingograph (Elema Schönander Solna, Sweden)

F the pectrographic analyses the ailable pparatus was the V iceprint (Voiceprint Inc., New Jersey)

This sound spectrograph pro des visual patterns, sound spectrograms, of the different ac tic ttributes of th cry performance. The frequency measured n the ertical axis, 0—5000 H from bott m to t p. In some high-p t hed signals a frequency scale of 0—8000 Hz was used Th d ration was measured on the horizontal axis, from left t right, and one spectro-gram-print comprises 2.4 seconds The writer was syncronized with a narrow band filter 45 Hz.

After painful stimulus the first phonation, defined as "the total vocalization during one inspiration or expiration" (115) was analyzed spectrographically

The spectrograms were all made under the supervision of the same phonetician, V Vuoren koski, at the Department of Speech Communication (Head prof. G Fant) Royal Institute of Technology (KTH) Stockholm.

C. CHARACTERISTICS OF CRY SOUND

Th following characteristics tudied in the cry-signals are, to great extent, the attributes used in previous in estigation and described in 1966 (69) 1968 (115) and 1970 (61) However the characteristics of tenseness and nasality of signals were omitted, because these cannot be seen on the pectrograms in high-pitched signals. The present study also included measurements of rapid change f pitch, "gliding" and vibrato.

Latency period the time interval between pain stimulus and onset of crying was measured in 0.1 seconds.

Duration f the phonati n was measured in 0.1 seconds. If signals exceeding 0.4 seconds occurred then only the time from the start of the first to the end of the last signal of 0.4 seconds, o longer was included in the measurements.

Durat on f the crying period was measured after one timulus and differentiated int durations of under and over 30 seconds.

Second pause was the time interval between the

first and second vocalization and was noted if the duration exceeded 1 second.

Voice The cry can be voiced or voiceless The *voiced* phonation consists of pure tones of a single frequency From such sounds a repeating pattern of waves can be observed on the spectrogram. The lowest line shows the fundamental frequency and the overtone frequencies are exact multiples of the fundamental frequency (34 38, 71) If the phonation is *voiceless* it consists of a blur of indistinguishable vibrations. A *halfvoiced* phonation consists of voiced and voiceless parts The voiceless part was noticed if the duration exceeded 0.2 second as in Fig 1 a.

Shift Sudden shifts of fundamental frequency have been noticed if their duration exceeded 0.2 seconds The phonation may initiate or terminate with a shift The shift can also be in the middle of the phonation, when we see a sort of double shift Spectrograms with shifts are seen in Figs 1 c and 1 g In phonations with shift, the part of the phonation which was of shorter duration was counted as the shift part

Pitch The highest measured voiced point of the fundamental frequency was the *maximum pitch* the lowest measured voiced point the *minimum pitch* The *maximum pitch of shift* was measured separately if the duration of the shift exceeded 0.2 seconds, otherwise it was included in maximum pitch

Melody types. The change in pitch level stimulated the melody type, which could be *falling rising falling rising falling-rising* or *flat* The type of cry was falling or rising when there was at least a 10 per cent change in pitch level during more than 10 per cent of the duration of the signal. The cry-signal could also be without any melody form when the phonation was totally voiceless or consisted only of glottal plosives.

Glottal plosives were seen as short phonations in the spectrograms, as in Fig 1 f and their occurrence was noted in the cry-analyses.

Continuity of signal The phonations were classified as continuous if there was a single short signal or if only one signal exceeded 0 4 seconds.

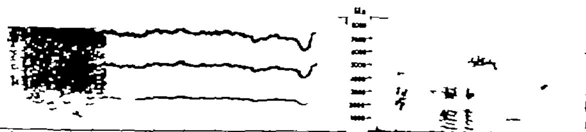
Glottal roll (vocal fry) was seen in the spectrograms as vibrations of low intensity often at the end of the phonations as in Fig 1 d. The occurrence of glottal roll was included in the measurement if the duration was at least 0.2 seconds

Vibrato was seen as wave-like changes of pitch, as in Fig 1g

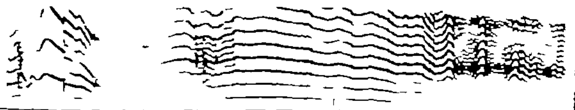
Double harmonic break and *bi-phonation* occurred in the spectrograms as lines of extraneous noise and were noted in the analyses if they lasted over 0.2 seconds The *double harmonic break* which is another simultaneous series of harmonics (115) follows in intensity the fundamental tone and its harmonics In *bi phonations* there are two different sound sources (111) and in the spectrogram the bi-phonation lines are not parallel with the fundamental tone. Figs 1d and 1g show double harmonic break and Fig 1e and 1f biphonation.

Gliding a change of pitch of 600 Hz or more per 0 1 seconds, was measured in the phonations and demonstrated in Fig 1f

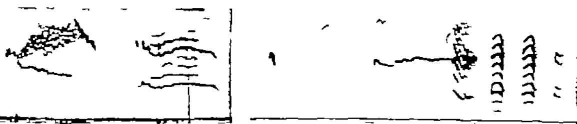
FIG. 1 *Spectrograms demonstr ting different cry-characteristics*



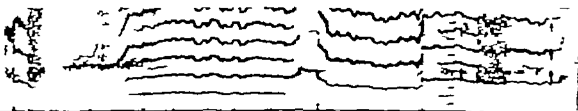
a. A cry-signal from newborn infant, b. 3200 g 39 g. ith peripheral respiratory distress. The sound spectrograph was calibrated to frequency range of 0—5000 Hz, usually used in the present investigation. The signal starts ith oiceless part of 0.8 sec., and ends in oiced phonation ith flat type of melody
b. In some phonations frequency range of 5000 Hz was not sufficient to include all high-pitched parts and an upper range of 8000 Hz was used, as here. This signal is from newborn ith peripheral respiratory distress (b.w. 3190 g 33 g.), but the infant also had tremor and some hypotonia at time of recording.



c. An example of shift, sudden change in fundamental frequency in cry from premature ith IRDS (b.w 2180 g 36 g.w.).
d. Glottal roll is seen as narrow harmonics of low intensity at the end of this phonation from newborn infant (b.w 1580 g 38 g.w.) Double harmonic break occurs near the beginning.



e. Bi-phonation, lines of extraneous sound patterns not parallel with the fundamental tone, occurs in this phonation from full-term infant with central type of respiratory failure (b.w. 3740 g).
f. The spectrogram show gliding at the beginning of the phonation, and also in the bi-phonation-part at 0.9—1.2 seconds. Glottal plosives occur at the end of the signal. Newborn ith central respiratory failure, b.w 3300 g 41 g.w



g. Vibrato in signal from newborn ith congenital heart disease (b. 2970 g 39 g.w). A shift seen at 1.3 sec., and often, as here, the fundamental tone has shifted to continue from one of the upper harmonics. Double harmonic break occurs near the end.

RESULTS

The results are based on the analyses of pain induced cries in 310 infants, 0—10 days old who, on the basis of clinical data, were divided into two main groups (I) symptomless low birth weight *neonates and (II) newborn infants with signs of* asphyxia at and/or immediately after birth.

The low birth weight infants were divided according to gestational age into 3 different groups (38—40, 35—37 and 34 g.w.) In the cry analyses of the asphyxiated infants the crying of the newborn with peripheral and of those with central types of respiratory failure or distress were analysed separately

The results of the cry-analyses are summarized in Tables 5, 7 and 8.

The cumulative percentage distribution of minimum and maximum pitch are seen in Figs 2, 4 and 5.

A. GROUP I LOW BIRTH WEIGHT NEONATES

Cries from 105 low birth weight infants, 30 small-for-date and 75 premature, were analysed. Of the premature infants 35 were born within 35—37 weeks of gestation and 40 before 34 completed weeks of gestation.

1 Small for-date neonates

The cry-characteristics of the small for-date infants were compared to the crying of 50 full term healthy newborn infants, the reference material, with birth weights over 2500 grams, as listed in Table 5

No significant differences were observed in the following characteristics the latency period, the duration of the crying period and occurrence of second pause. The prevalence of voiced and continuous signals was practically equal in both groups. *Neither were there significant differences* in occurrence of double harmonic break, bi phonation, glottal roll and vibrato. No gliding was observed in either group The dominating melody types were the falling or rising falling.

Significant differences between the crying of healthy full-term newborn infants and the small-for-dates occurred in the duration of the phonation, which was longer in the crying of the small for-date neonates The medians of the minimum and maximum pitches revealed significantly lower pitch frequencies in the small-for-dates. Shift and glottal plosives occurred less frequently in the crying of these infants. The maximum pitch of shift was increased.

Spectrographic examples of small for-date infants cries are seen in Figs 1d and 3b and for comparison, in Fig 3a a spectrogram of a cry signal of a full term healthy infant with normal birth weight.

2 Premature infants

Table 5 shows the results of cry-analyses of the premature infants, separately for those with a gestational age of 35—37 weeks and for those with a gestational age $\leq$ 34 weeks. The results were compared to the crying of 50 full-term healthy infants with normal birth weights.

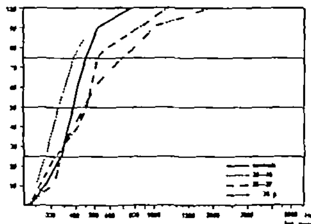
No significant differences were observed in the following cry-characteristics of the premature infants, irrespective of gestational age the la

TABLE 5. *The prevalences ( ) medians (Md) and quartiles (Q1 Q3) of different cry-characteristics in symptomless low birth weight neonates and controls*

Variable		low birth weight neonates: small-for-date	low birth weight neonates: prematures 35—37 g.w.	low birth weight neonates: prematures ≤34 g.w.	controls: full-term >2500 g
	No.	30	35	40	50
Latency period, sec.	Q1	1.4	1.4	1.3	1.2
	Md	1.7	1.8	1.6	1.8
	Q3	2.2	2.5	2.0	2.5
Duration of phon., sec.	Q1	2.2	1.8	1.3	1.6
	Md	3.8	3.1	2.4	2.0
	Q3	4.9	4.9	3.5	3.6
Crying period > 30 sec., %		27	20	15	20
Second pause, %		17	34	38	34
Minimum pitch, Hz	Q1	280	320	340	340
	Md	330*	460	450*	390
	Q3	390	520	710	450
Maximum pitch, Hz	Q1	470	580	600	580
	Md	550*	740*	1040***	620
	Q3	630	1240	1910	690
Shift, %		13	43	28	32
Maximum pitch of shift, Hz	Md	1850**	1830*	1200	1100
Voiced phonations, %		50	49	53	66
Continuous signals, %		63	66	69	68
Melody type, %					
falling		60 } 94	46 } 83	33 } 85	63 } 85
rising-falling		34	37	52	22
rising		— } 6	3 } 17	5 } 15	— } 10
falling-rising		3	3	7	7
flat		3	11	3	3
No melody type, %		— —	— —	—	5 5
Gliding, %		—	11	18*	—
Double harmonic break, %		33	29	25	44
Bi-phonation, %		—	14	5	—
Glottal roll,		57	43	43	60
Vibrato,		7	6	3	—
Glottal plosives,		18*	9*	3***	40

significance level
*p < 0.05
**p < 0.01
***p < 0.001

Significance levels are based on Wilcoxon-test (continuous variables) and χ^2-test (discrete variables). They refer to differences between the characteristics in low birth weight infants and controls.



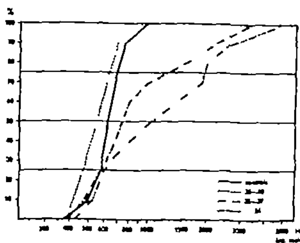


Fig. .. The cumulativ percentage distribution of minimum and maximum pitch in low birth weight infants and controls.

tency period the duration of the phonations and the crying period, the occurrence of second pause shift, double harmonic break, glottal roll and vibrato. An increase in minimum pitch in those with a gestati nal age of 35—37 weeks was observed when compared with crying of the full-term the differences, however were not tatistically significant. Voice and continuity of als, as also the same melody type, occurred ally often in all groups. Significant differences etween bi-phonation and maximum pitch of shift did not occur between those with a gesta tional age ≥ 34 weeks and full-term controls

Significant differences were observed in the following cry-characteristics. The minimum pitch of the cry-signals of infants with a gestational age ≤ 34 weeks was increased The maximum pitch was significantly increased in all prematures irrespective of gestational age, the values highly significant in those with a gestational age ≤ 34 weeks The maximum pitch of shift was higher in those with a gestational age of 35—37 weeks, and these infants also had significant increase in occurrence of bip-honations The occurrence of glottal plosives was less frequent, irrespecti e of gestational age. Gliding occurred ignificantly more often in the prematures

Spectrograms of premature infant cries are seen in Fig. 3c, 3d, 3e and 3f All the figures were reduced according to the same scale.

3. *The typical cry signal of symptomless newborn infants*

The typical cry-characteristics in symptomless neonates, full-term and premature, can be classified as follows, using the interquartile range for the continuous variables

— the latency period 1.2—2.5 seconds.

— the duration of the phonations 1.3—5.0 seconds

— a second pause ≤ 4.0 seconds

— the minimum pitch of fundamental frequency 300—450 Hz in full-terms and 300—600 Hz in prematures.

— the maximum pitch of fundamental frequency 500—700 Hz in fullterms and 600—1500 Hz in prematures.

— the maximum pitch of shift ≤ 1500 Hz in full-terms ≤ 2000 Hz in prematures

— a relatively stable signal with no sharp changes in pitch

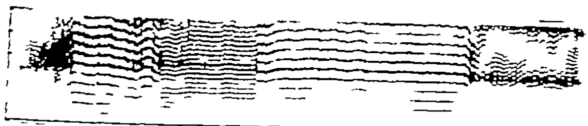
— no gliding.

— no bi phonation.

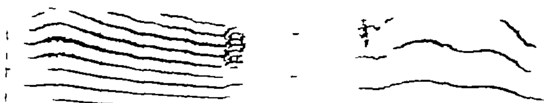
— a falling or rising falling melody type.

Because the interquartile range was used some deviation from this pattern occurred in duration and pitch measurements of crying in healthy infants. Some spectrograms revealed gliding and/ or bi-phonations. A rising falling-rising or flat melody type occurred in a few signals. Therefore a count was made of the number of "abnormal"

FIG. 3. *Spectrograms of th cry g of symptoml eow born r w uneventful pregnancies and deliveries*

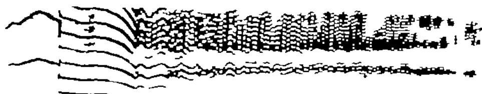


a. A cry-signal from full-term healthy infant, (b.w 3 70 g 4 g) th ela h stable fundamental frequency of about 500 Hz, shift near the middle and glottal roll at the end of the phonation.

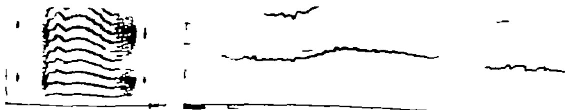


b. A signal from small-for-date newborn (b.w 2340 g 39 g.w). The fundamental tone ppears shorter on the spectrogram because of low sound pressure at the beginning and the end. When most of the pain cry signals are tense, the intensity of the upper harmonics is increased, as here

c. A cry-signal ith rising-falling melody t pe in premature, b.w 1780 g/33 g. The maximum pitch is 1900 Hz, hich is higher than that seen in the cry of any full-term healthy newborn.



d. A relatively common type of cry-signal in the symptomless neonate. This phonation from premature (1900 g/37 g. .) has shiftpart followed by falling type of melody and glottal roll at the end of the phonation.



and f. Cry signals from tw different prematures, both born after 29 g.w and th birth eights of 1200 g and 1270 g respectively) A relatively low pitched phonation in small prematures occurred only if they are symptomless at birth. (f) A high-pitched cry in small prematures can sometimes be hard to differentiate from the cry of asphyxiated newborn prematures

TABLE 6. *The occurrence ( ) of "abnormal" cry characteristics in the same cry signal in newborn infants of different gestational age groups*

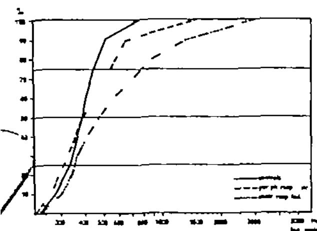
number of abnormal characteristics		full-term		premature	
		>2500 g	≤2500 g	35—37 g.	≤34 g.w
	No.	50	30	35	40
0		6	57	54	50
1		22	37	23	35
2		2	6	23	10
3		—	—	—	5
4		—	—	—	—
5 or more		—	—	—	—

characteristics in the same signal, and the results are seen in Table 6.

In two premature infants three abnormal characteristics occurred in the same signal. These neonates were both small prematures with a gestational age of 30 and 32 weeks and birth weights of 1300 and 1480 grams respectively.

B. GROUP II. ASPHYXIATED NEONATES

Because it had been observed that the crying of symptomless newborn infants differed according to gestational age, the cry-signals of full term and premature were analysed separately for the asphyxiated neonates. The results of the cry-analyses are seen in Tables 7 and 8, and Figs 4 and 5 show the cumulative percentage distribution of minimum and maximum pitch. Figs 6, 7 and 8 show spectrograms of crying of asphyxiated neonates.



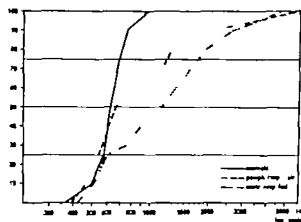
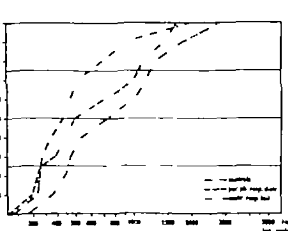


Fig. 4. The cumulative percentage distribution of minimum and maximum pitch in full-term asphyxiated neonates and controls.



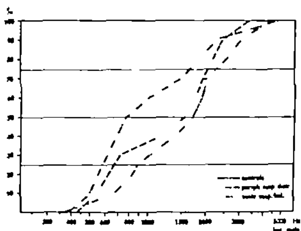
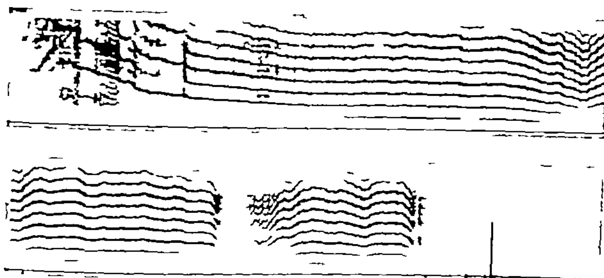


Fig. 5. The cumulative percentage distribution of minimum and maximum pitch in premature asphyxiated neonates and controls.

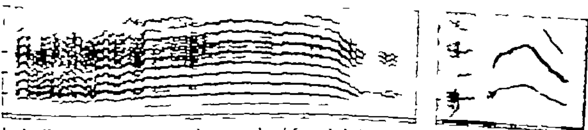
FIG. 6. Spectrograms of crying neonates (\ g er her I respiratory distress



a. A cry-signal of long duration in newborn infant ith peripheral respiratory distress (b. 3200 g 40 g.). A shift part with short bi-phonation occurs at the beginning but the rest of the phonation has relatively stable configuration.



b. A phonation ith rising-falling melody type from newborn (b.w 1700 g 35 g.) he died of pulmonary atelectasis and hyaline membranes.
c. A rising-falling type of cry from an infant he rapidly recovered from the respiratory distress. This type of high-pitched phonation does not differ from the crying of mptomless prematures, as seen in Fig. 3c.



d and e. High pitched and short cry-signals in tw newborn infants, ho both died in the neonatal period,
(d) full-term with b. 2980 g. he died of pulmonary haemorrhage with cry like that of healty neonate,
(e) premature (b.w 1780 g 35 g. .) ith hyaline membranes at autopsy. Note the unusual configuration in the spectrogram at the beginning of the last signal.

1 Neonates with dominating peripheral respiratory difficulties

The cry-analyses of 40 full-term and 40 premature infants with mainly peripheral respiratory distress were compared with the crying of 50 full-term and 75 premature symptomless neonates, respectively

No significant differences occurred irrespective of gestational age in duration of the latency period occurrence of second pause, double harmonic break, glottal roll, gliding and vibrato Neither did ignificant differences occur in voice and continuity of signals or in occurrence and maximum pitch of shift The increase in rising falling rising and flat types of melody in the full-term asphyxiated neonate was not significant nor were the differences in minimum pitch or occurrence of glottal plosives ignificant

Significant differences occurred in duration of the phonations which was longer in the neonates with peripheral respiratory distress, and also in the duration of the crying period which was increased The maximum pitch was significantly higher in those with peripheral respiratory distress bi-phonations occurred significantly more often. Minimum pitch was increased in the asphyxiated prematures, who also showed an increase in the occurrence of glottal plosives

Three full-term neonates had tremor after the first day of life, and these infants were the only ones in this group with a minimum pitch above 800 Hz and a maximum pitch above 1200 Hz, an occurrence not observed in controls. Two of these infants died in the neonatal period of congenital heart disease, one of them had muscular rigidity at the recording made one day before death Two more full-term infants died of respiratory disorders. They had not sh wn any abnormal characteristics in their crying Twelve premature infants died of pulmonary disorders in the cry signals of 4 f these a high fundamental frequency occurred with minimum pitch > 1000 Hz and a maximum p t l > 2000 Hz, both rare in controls. Rising, falling rising or flat melody type and/or bi phonati w seen in 6 signals. In 5 phonations comparis n with controls showed no differences.

2 Neonates with dominating respiratory center failure

To this group belonged 70 full term and 55 premature neonates and the results of the cry analyses were compared with the crying of 50 full-term and 75 premature symptomless neonates respectively

No significant differences were seen in occurrence and maximum of shift voice and continuity of signals and in occurrence of double harmonic break and vibrato

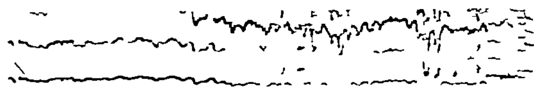
Comparison with controls showed no significant differences in duration of the latency period or in the occurrence of second pause in full-term asphyxiated neonates, nor in the occurrence of gliding, glottal roll, glottal plosives or the duration of the crying period in asphyxiated prematures.

Significant differences were observed in the duration of the phonations, which was increased in the asphyxiated full-term and decreased in the asphyxiated premature. In these prematures a second pause occurred ignificantly more often, and the duration of the latency period was also increased. In the full-term asphyxiated neonates gliding occurred more frequently and glottal plosives and glottal roll less frequently than in controls. Full-term asphyxiated neonates cried for longer periods.

In all newborn infants with respiratory center failure the minimum and maximum pitch of fundamental frequency were, regardless of gestational age, significantly increased as also the occurrence of rising, falling rising and flat types of melody Bi-phonation occurred ignificantly more often in the asphyxiated newborn infants.

Fifteen neonates died of cerebral haemorrhages 4 of these were full-term and 11 premature. Three of those who died had cry-signals which could be characterized as normal. All 4 full-term neonates who died had "abnormal" cry signals with a rising or flat type of melody and a minimum pitch above 800 Hz and/or a maximum pitch above 1200 Hz, not observed in controls. Of the 11 prematures who died, 8 had cry signals with a minimum pitch above 1200 Hz and a maximum pitch above 1800 Hz, both rare in

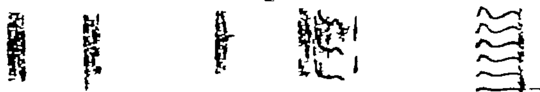
Fig. Spectrograms of cry signals from neonat r at en al typ f physia



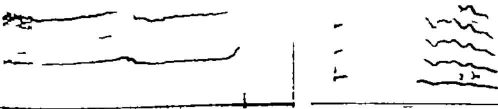
a. A high-pitched signal ith ibrato of an unusually high hange in pit h from neonate, b. 3390 g 38 g. Apgar 3— healthy at check-up.



b. A cry-signal showing unstable pitch ith man shifts in neonate with b.w 3990g, 40 g.w.. Apgar 4—6, healthy at control,
c. A cry-signal from an asphyxiated newborn ith Dow syndrome b.w 2360 g 39 g. Apgar 6—6.



g. A cry from an infant with 13—15 trisomy b. 2300 g 40 g. Apgar 6—6, the last signal consisting of an inspiration-expiration-inspiration cry
e. An inspiratory cry-signal, seen in few cases of those ith central type of asphyxia. The inspiratory signals are not further separated or discussed. B. 3300 g 40 g. Apgar 3— retarded at follow-up.



f. A cry-signal from full erm sphyxiated neonate b. 4300 g 38 g.w Apgar 3—6, show high-pitched phonation with rising melo l ype. The infant died at the age of 4 day of cerebral haemorrhage
g. A cry-signal from premature b. 1780 g 34 g. Apgar 3—4, ho died of intracranial haemorrhage. The signal has falling type of melody more common in the cry of healthy newborn. A short biphonation (< 0.. sec.) not included in the measurements, occurs in the signal. A short bi-phonation might later prov to be of importance.

DISCUSSION AND CONCLUSIONS

A. SIGNIFICANCE OF DIFFERENT CRY-CHARACTERISTICS

The present investigation concerned pain-induced crying in newborn infants. Only the first phonation after pain stimulus was selected for the analysis, a procedure also followed in previous investigations by our research group (61 67 69 110, 114 115). Similarities in the phonations of the same infant (66, 97) indicate, that this procedure can be accepted.

Some characteristics which did not show significant differences in the infant groups studied could be omitted in later investigations and are not further discussed in comparing crying of the newborn in the different groups. These are voice quality and continuity of signals occurrence of shifts and vibrato Neither were the differences in occurrence of double harmonic break, glottal roll and glottal plosives considered important, as these characteristics also differ in cry-signals of healthy infants (115)

The occurrence of shifts double harmonic break, bi-phonations and glottal roll were included in the measurements only if they lasted over 0.2 seconds. These characteristics might in later investigations be found of importance even if of shorter duration. This concerns especially the occurrence of shifts and bi-phonations Also in duration measurements of th phonation, if signals exceeding 0.4 se nd occurred they formed the boundary for tl gnals that were counted in measurements f l n and conti nuity of signals. It is, as W H kert et al. declare (115) "more time-cons t measu e the whole phonation during on tion, but this might correlate better with different neonatal disorders.

The occurrence of a second pause was noted if the duration exceeded one second. However second pauses exceeding 4 seconds occurred mainly in small prematures and asphyxiated neonates and this cry-characteristic might be of more practical interest when counting only longer second pauses.

Based on the present investigation the following characteristics were considered important and will be discussed below *latency period* and *second pause duration of phonation* and the *crying period* the *minimum and maximum pitch* and *maximum pitch of shift* the *melody type bi-phonation* and *gliding*

Thus of the 17 cry-characteristics analysed, 10 presented significant differences in at least one of the infant groups studied compared to controls. Also phonations of *unstable pitch* were found almost exclusively in the crying of asphyxiated neonates.

B CHARACTERISTICS OF CRY IN LOW BIRTH WEIGHT NEONATES

The fundamental frequency of vocalization in newborn infants has been found to comprise values between 380—650 Hz (9 66, 72, 73, 87 96, 115) and said to decrease at a constant rate during life (83) being in men 98—146 Hz and in women 196—295 Hz (8)

The crying of healthy small-for-date neonates greatly resembled that of full term infants with birth weights over 2500 grams In comparing the

cry-signals of these two groups a significant decrease was found in fundamental frequency of the small-for-dates. The upper limits of minimum and maximum pitch were however quite similar and it is the increase in pitch which is important in comparing the crying of healthy and sick neonates.

In prematures the fundamental frequency increased with prematurity and even some very high-pitched signals were found.

The interquartile range was used in the continuous variables for a definition of normal cry signals. In the full-term newborn no cry-signal showed a minimum pitch above 800 Hz and a maximum pitch above 1200 Hz. This, as well as the quartile point, could be used as limit for normality. In premature infants however a few very high-pitched signals occurred (> 2500 Hz) and it was considered more practical to use the quartiles. Thus, even in normal signals some abnormal characteristics occurred, and this seemed an indication for counting the number of abnormal attributes in each signal.

A typical cry-signal of the healthy full-term newborn is clearly recognizable. In prematures there were some high-pitched or short phonations, which were sometimes hard to differentiate from the crying of asphyxiated prematures. Here the counting of abnormal characteristics in the signal can be useful, when the signals of healthy neonates often had a falling or rising-falling melody and biphonation or gliding seldom occurred.

C. SIGNIFICANCE OF ABNORMAL CRY IN ASPHYXIATED NEONATES

All the cries of the asphyxiated newborn were recorded within the first 3 days of life, 90 per cent within the first day. It is not known how fast the possible abnormalities in the cry-signals of asphyxiated neonates disappear after birth. In the present study some cries, recorded at 2–3 days of age, might have been more abnormal at birth. Some of the phonations of the asphyxiated newborn have not, at the age of 1–3 hours, differed from the crying of healthy neonates. This often applied to those who recovered rapidly from the asphyxia and had Apgar scores above 7 at 15 minutes of age.

An increase in fundamental frequency has been noticed in previous investigations concerning brain-damaged infants (61, 70, 114, 115) and those with chromosomal aberrations (9, 3, 72, 86, 110, 115).

In the present investigation significantly more high-pitched signals occurred in the asphyxiated neonates than in the controls. A pitch above the upper quartile of crying in symptomless neonates was considered abnormal. The most high pitched signals were often in the most damaged neonates; therefore it seems that future studies should differentiate between the varying degrees of increased pitch.

According to the literature, significantly longer latencies have previously been found only in infants with severe brain damage (27, 57, 69). In the present investigation significantly longer latency periods occurred only in prematures with the dominating central type of asphyxia. The pain stimulation was applied when the neonates were in the clinical state 2–3 according to Prechtl and Beintema (95). The clinical state of the newborn might especially influence the latency periods, which has been found to shorten with repeated stimulation (32), but also the crying periods. The increase in the crying periods in the present study could possibly be attributed to irritability caused by disease, and in those with peripheral respiratory distress the "grunting" also extended the crying periods.

The increase in duration of the phonations seems to be an important criteria, especially in differentiating the signals of those with peripheral respiratory distress, since long cry-signals often could be the only characteristic that was different from the cry of symptomless neonates.

A significant difference occurred in the melody type in those with dominating central respiratory failure. The increase in rising, falling-rising and flat types of melody and also the increase in fundamental frequency and in occurrence of biphonation and gliding seem to be the most important criteria in differentiating the crying of

those with dominating central type of asphyxia from symptomless neonates.

A typical cry-signal with 0—2 abnormal characteristics as defined above, occurred in 100—97 per cent of the symptomless neonates full-term and premature, respectively The typical cry signal occurred in 75—73 per cent of those with dominating peripheral respiratory distress and in 43—46 per cent of those with dominating central respiratory failure. Ten of these neonates died of peripheral respiratory disorders 4 of cerebral haemorrhages Four infants had brain damage at follow up. Thus, *if the cry signal in the asphyxiated neonate was similar to that of a symptomless newborn severe peripheral respiratory distress with subsequent death could occur but a severe central type of asphyxia with death or later sequelae was seldom seen to follow*

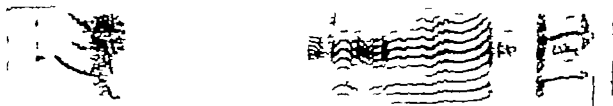
Abnormal cry-signals occurred in 25—27 per cent of those with dominating peripheral respiratory distress and in 57—54 per cent of those with dominating central respiratory failure. Of those 44 neonates with 4 or more abnormal cry characteristics, 8 had peripheral respiratory distress and 36 central respiratory failure. Thus *with asphyxia the changes in the characteristics of crying increased with the severity of asphyxiation and especially if the central type of asphyxia was dominant.*

D CLINICAL USEFULNESS OF CRY STUDIES

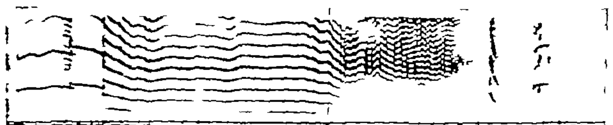
The results from the present investigation show that significant differences do exist in the crying of healthy full-term neonates compared to that f symptomless prematures and also of those with asphyxia at birth irrespective of gestational age. However new investigations are still needed to correlate the cry attributes to different neonatal disorders.

The cry-analyses might be helpful *in finding those risk group infants who would later need neurological observation* For example, Figs 9 and 10 show the spectrograms of cries from a pair of twins, who both had a central type of asphyxia after birth. The "cry print" (106) of one twin was normalized when leaving hospital and the child was healthy when checked at two years. The other twin still had an abnormal cry-signal when leaving

FIG. 9. a and b. Two cry signals from the same neonate (twin-pair b.w. 2320 g/38 g.w. Apgar 6—6) with central type f respiratory failure

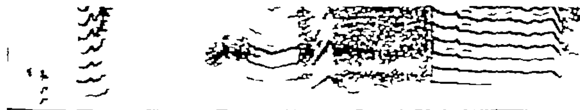


a. Cry signal recorded at 3 hours of age show falling-rising type of melody with high pitched phonation and short biphonation.

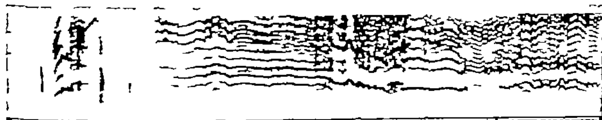


b. A cry-signal recorded 2 ed ter show more normal configuration ith falling melody type, shift at the beginning and glottal roll at the end of the p ation

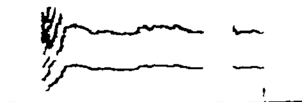
Fɪɢ 10. and b. Two cry-signals from the twin-partner to infant mentioned in Fig 9 (b.w. 2180 g 38 g.w. Apgar 5—7), ith central respiratory failure



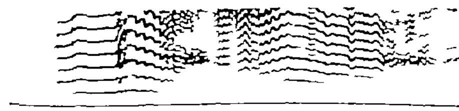
a. The phonation starts with short bi-phonation and another short signal ith rising melody form. The last signal has some instability in fundamental frequency



b. A relatively long cry-signal from the same infant at 2 eeks of age. The spectrogram shows high-pitched parts and bi-phonation in an unstable signal. The infant had Larsen syndrome at control.



Fɪɢ. 11 Two spectrograms of the same newborn with peripheral respiratory distress (b.w. 3100/40 g.w.) at ( ) 4 hours and (b) 5 days of ge. These tw spectrograms show the change in the infant cry-characteristics of pitch and melody type which occurred when the infant recovered from the disease.



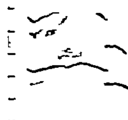


FIG. 1_. *Two spectrograms from a symptomless premature (b.w. 2100 g/34 g.w.) at ( ) one day and (b) 5 weeks of age. The figures show how the short high-pitched phonation is of longer duration and lower pitch hen the infant was regarded as full-term.*



hospital and this infant had convulsions and was mentally retarded at the follow up

In cry-analyses of infants with peripheral respiratory distress the cry-analyses can be helpful *in judging the severity of disease* Fig 11 shows how the cry-characteristics of an infant with hyaline membrane disease become more normal as the infant recovers.

In the crying of premature infants the cry characteristics changed more in accordance with gestational age than with birth weight, and the cry-analyses can probably be an additional tool *in estimating gestational age* since the cry becomes more high pitched in small prematures. The differences in the crying of premature infants did not seem to be influenced by the stage of gestation at which delivery took place. Thus an infant, born at 34 gestational weeks, showed at 40 weeks the same cry-characteristics as another infant, born full-term, as demonstrated in Fig. 12.

The sound spectrographic studies are time-consuming and need the supervision of specially trained persons. The phonetician, V Vuorenkoski, who, since 1961, ha been working with spectrographic analyses of infant crying taught the author the technique f these analyses. At the end of the study we t geth r checked the most complex spectrogram Thirty random sampled spectrograms were l analyzed independently and no significant [illegible] rences occurred (Tables 13 and 14) This in [illegible] that, although a research group studying [illegible] cries should use a specially trained phonetician a clinician in a pediatric hospital is able to learn the requisite technical knowledge, and "the permanent acoustic recording of cry-sound as of heart sound, could conceivably become a standard feature of the clinical archives" (66)

Table 13. Reliability of measurement quantitati attributes

Attribute	No.	S_Δ	$\bar{}$	S%
Min. pitch, Hz	29	27	749	3.6
Max. pitch, Hz	29	46	1494	3.1
Pitch of shift, Hz	6	13	1813	0.7

No = number of signals measured by both judges
S_Δ = standard deviation of measurement error
$\bar{}$ = common mean of the series
$S\%$ = S_Δ as per cent of $\bar{}$

Table 14. Reliability of measurement qualitati attributes (comparison between tw observers)

Attribute	No.	Number of attribute classes	Relati freq. of concordant ratings
Glottal roll	30	2	1.00
Melody type	30	5	0.80
Continuousness	30	2	0.97
Voicelessness	30	3	0.97
Double harmonic break	30	2	1.00
Glottal plosives	30	3	0.90
Vibrato	30	2	1.00

No. = number of signals rated by both judges

SUMMARY

The results are based on analyses of pain-induced cries in *310 newborn infants*, 0—10 days old, who were grouped as follows. The *first group* comprising *105 low birth weight neonates* born after uncomplicated pregnancies and deliveries was sub-divided, according to gestational age, into *small-for-date* (30 infants) and *premature* (75 infants). The *second group* comprised 205 neonates, 130 full-term and 75 premature who at birth had *symptoms of asphyxia*. The group was sub-divided into those having *dominating peripheral respiratory difficulties* (80 newborn) and those having a *dominating central type of respiratory failure* (125 newborn).

Additionally third group comprising *50 healthy full-term infants* under 10 days of age, formed a reference material for comparison of the cry-analyses results.

The pain-induced crying of the infants was recorded on tape and the first phonation after stimulus was analyzed. Measurements of latency period, duration of the phonations and second pause have been made with a direct writing oscillograph the other characteristics were analyzed spectrographically.

Seventeen different characteristics of cry sounds were analyzed.

In all infants, irrespective of gestational age or severity of disease, no differences of importance for further analyses occurred in the following characteristics prevalence of voiced and continuous signals, and occurrence of double harmonic break, shift, glottal plosives, glottal roll and vibrato.

Low-birth weight neonates

The cry-signal of the non-asphyxiated *low birth weight* neonates had, in 83—94 %, a falling or rising-falling type of melody with a relatively stable pitch. The median of the latency period was 1.6—1.8 sec. and the duration of the phonation 2.4—3.8 sec. The crying period lasted >30 sec in 15—2? of the cries. Smaller prematures cried for shorter period.

The crying of the *small for-date neonate greatly resembled that of the healthy newborn with normal birth weight* and those characteristics (duration of the phonation and pitch of fundamental frequency and shift) in which significant differences occurred do not seem to be of importance for future analyses.

The median value of minimum pitch was 330 Hz, of maximum pitch 550 Hz and of maximum pitch of shift 1830 Hz. No signal had minimum pitch >800 Hz and a maximum pitch >1200 Hz. Gliding and bi-phonation did not occur.

The *premature neonates* were separated into those born after 35—37 and those born ≤ 34 gestational weeks. The crying in one or both of these premature groups *differed significantly* from the full-term control group in the following characteristics ***minimum*** and ***maximum pitch of fundamental frequency maximum pitch of shift*** and occurrence of ***bi-phonation*** and ***gliding***.

The signals were more high-pitched the more immature the neonate, the increase in minimum pitch was significant in the smaller prematures

(med. 450 Hz) The maximum pitch was significantly increased in all prematures irrespective of gestational age (med. 740 Hz and 1040 Hz) the maximum pitch of shift in the 35—37 gestational age group (med. 1830 Hz). The occurrence of gliding increased significantly in all prematures (11—13 %), bi-phonation only in the 35—37 gestational age group (14 %)

Asphyxiated newborn infants

In both groups of asphyxiated newborn infants the cry-signals of the full-term and premature were analyzed separately

The crying of neonates with dominating *peripheral respiratory distress differed significantly* from the controls in the following characteristics the *duration of the phonation* (increased to med 4.5 sec. in full-terms, 3.4 sec. in prematures) and the *crying period* (increased to >30 sec. in 53 % of full terms 35 % of prematures) the *maximum pitch of fundamental frequency* (increased to med. 640 Hz in full-terms, 1590 Hz in prematures) and occurrence of *bi-phonation* (increased to 20—25 %) The *minimum pitch* was also significantly increased in the asphyxiated prematures (med 490 Hz)

The crying of neonates with dominating *central respiratory failure differed significantly* from the controls in the *duration of the phonation* (increased to med. 3 7 sec. in full-terms, decreased to 1 7 sec. in prematures) in the *minimum and maximum pitch* (increased to med 470 Hz and 1120 Hz in full-terms, to 720 Hz and 1700 Hz in prematures), occurrence of *bi phonation* (increased to 26—27 %) and in the *melody type* (increase of rising, falling rising and flat types of melody to 50—54 %) There was also an increase in *gliding* (14 %) and in the *crying period* (41 %) in the full term asphyxiated neonate. In premature asphyxiated neonates the *latency period* was increased (med. 2.0 sec.) and a *second pause* occurred more often (53 %)

Significance of abnormal cry-signals

In those cry-characteristics where the asphyxiated neonates differed significantly from the controls, the differences were often more marked the more severely the newborn had been asphyxiated These cry-characteristics were found in 0—3 % of symptomless neonates in 25—27 % of those with dominating peripheral respiratory distress and in 57—54 % of those with dominating central respiratory failure, full term and premature. Of the 19 neonates with the largest number of abnormal cry-signals, 3 died and 9 had neurological sequelae at follow-up.

The typical cry-signal, which occurred in 100—97 % of the symptomless newborn infants, was seen in 75—73 % of those with dominating peripheral respiratory distress and in 43—46 % of those with dominating central respiratory failure, full-term and premature. Ten of the 14 neonates who died of peripheral respiratory disorders had had a typical cry-signal. Of the 42 neonates with central respiratory failure who had either died or were found to have symptoms of brain damage at follow up, only 8 had the typical cry-signal of a symptomless neonate. Thus, *cry signals with the largest number of abnormal characteristics occurred in those with dominating central respiratory failure*, and the analyses of crying can in the future be one more criteria in estimating diagnosis or prognosis in asphyxia during the newborn period.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Professor *Ole Wasz-Höckert*, M.D., Head of the Department of Pediatrics, University of Oulu, who suggested to me the subject of the present investigation. His never failing interest and valuable advice throughout the study have been a great support.

I am grateful to Professor *John Lind*, M.D., Head of the Department of Pediatrics at Karolinska Sjukhuset, Stockholm, for constructive advice and valuable criticism during many stages of the study.

I also wish to thank Mr *V. k. Vuorenkoski* who gave valuable advice in phonetical matters, an area of prime importance.

I thank Professor *Heikki Pitkänen*, M.D., at the time of the study Chief of the Institute of Midwifery Helsinki and *Vilho Hirvensalo*, M.D., Chief of the neonatological unit at the same hospital for their inspiring interest during the cry recording session.

Mr *Timo Partanen*, M.Sc., and Mrs *Pirjo Fahlström* Institute of Occupational Health, Helsinki carried out the biostatistical treatment of the data.

Mrs *Katherine Partanen* M.A., and Mrs *Barbara Rikberg* revised the English manuscript.

Financial support was received from the Medical Society Finska Läkaresällskapet and the Sigrid Juselius Foundation.

REFERENCES

1. ALDRICH, C. A. & ALDRICH, M. M.: Babies are Human Beings. Macmillan Co. New York 1951
2. ALDRICH, C. A., NORVAL, M., KNOP, C. & VENEGAS, F The crying of newly born babies. J Pediat, 28: 665, 1949.
3. ALDRICH, C. A., SUNG, C. & KNOP, K.: The crying of newly born babies. I. The community phase. J Pediat, 26 313, 1945.
4. ALDRICH, C. A., SUNG, C. & KNOP, K. The crying of newly born babies. II. The individual phase. J Pediat, 27 89, 1945.
5. ALDRICH, C. A., SUNG, C. & KNOP, K.: The crying of newly born babies. III. The early period at home J Pediat, 27 428, 1945.
6. APGAR, V A proposal for new method of evaluation of the newborn infant. Anesth Analg, 32 260, 1953.
7 APGAR, V & JAMES, L.S. Further observations on the newborn scoring system. Amer J Dis Child, 104: 419 1962.
8. ARNOT H J. & LEITHAUSER, H. Die mittlere Sprechtonhöhe bei jungen und alten Menschen. HNO, 16 114, 1968.
9. BAUER, H. Phoniatrischer Beitrag zum Cri-du-Chat Syndrom. HNO, 6: 185, 1968.
10. BERRY M. & EISENSON, F J. The Defects in Speech. F S. Crafts & Co. New York 1947
11 BOSMA, J. & LIND, J Upper respiratory mechanism of newborn infants. Acta Paediat Scand, Suppl. 185 32, 1962.
12. BOSMA, J. F & SMITH, C. C. Infant cry A preliminary study Logos, 4 10, 1961.
13. BOUND, J P BUTLER, N R. & SPECTOR, W O Classification and causes of perinatal mortality Brit Med J, 2 1191, 1956.
14. BRAZELTON, T B. Crying in Infancy Pediatrics, 29 579, 1962.
15. BRODBECK, A. J & IRWIN, O C. The speech behavior of infants without families Child Develop, 17 145, 1946.
16. BUTLER, N R. & BO[illegible] D G Perinatal Mortality E & S Livingstone. Edinburgh 1963
17 CAMERON, J., LIVSON, N [illegible] Infant vocalization and their relation [illegible] mature intelligence. Science, 157: 331, 1967
18. CLOUGHTON, E. C. T: Some notes on vagitus uterinus. Brit Med J 4: 200, 1933.
19. CRAIG, W S.: Convulsive movements occurring in the first 10 days of life. Arch Dis Child, 35: 336, 1960.
20. CROTTY J. G. & KUEHNLE, L. W: Vagitus uterinus in twin pregnancy Am J Obstr Gyn, 5 977 1948.
21. DESMOND, M. M., RUDOLPH, A. J & PHITAKSPHRAIWAN, P The transitional care nursery: A mechanism for preventive medicine in the newborn. Ped Clin N Amer 13 651 1966.
22. DRAGE, I. S. & BERENDES, H. Apgar scores and outcome of the newborn. Ped Clin N Amer 13 635, 1966.
23. DRAGE, I. S., KENNEDY C., BERENDES, H., SCHWARZ, B. K. & WEISS, W The Apgar score as an index of infant morbidity Dev lop Med Child Neurol, 8: 141, 1966.
24. FAIRBANKS, G. An acoustical study of the pitch of infant hunger wails. Child Devel, 13: 227 1942.
25. FISICHELLI, V R., COLE, M., ROSENFELD, R., HABER, A., DAVIS, J. & KARELITZ, S. The phonetic content of the cries of normal infants and those with brain damage. J Psychol, 64 119, 1966.
26. FISICHELLI, V R., HABER, A., DAVIES, J. & KARELITZ, S. Audible characteristics of the cries of normal infants and those with Down syndrome. Percept Motor Skills, 23: 744, 1966.
27 FISICHELLI, V R. & KARELITZ, S. The cry latencies of normal infants and those with brain damage. J Pediat, 62 724, 1963.
28. FISICHELLI, V R., KARELITZ, S., EICHBAUER, J & ROSENFELD, L. S. Volume-unit graphs Their production and applicability in studies of infants cries. J Psychol, 52 423, 1961.
29. FLATAU, T S. & GUTZMANN, H. Die Stimme des Säuglings. Arch Laryng Rhinol, 18 139, 1906.
30. F[illegible] D Maternal recognition of infant cry Develop Med Child Neurol, 9 293, 1967
31. GESELL, A. & ILG, F F Infant and Child in the Culture of Today Harper & Brths. New York 1943.
32. GLEISS, J & HOHN, W Das Verhalten beim Schreien nach konstanter Schmerzreizung atemgesunder und atemgestörter Neugeborener Deutsch Z Nervenheilk, 194 311, 1968.

33. Goutteyc, S., Vallancien B. & Leroy Boisivon, A. La oix des mongoliens. J Franc Otorhinolaryng, 16 139, 1967

34. Greene, M. C. L. The Voice and its Disorders, Sec. Ed. Pitman Med Publ. London 1964.

35. Greene, M. C. L. & Co ay J: Learning to talk: A study in sound of infant speech dev lopment. Folkway Records (N.Y.), FX 6271 1963.

36. Grenberg, M., Vuorenkoski, V. Partanen, T. J. & Lind, J.: Behavior and cry patterns in the first two hours of lif in early and late clamped newborn. Ann Paediat Fenn, 13 64, 1967

37. Grenier, G. F & Dillenschneider, E. Lrtude sonographique comparativ du syndrome du cri du chat J Franc Otorhinolar 16: 111 1967

38. Hadding-Koch, K. & Petersson, L.: Experimentell foortik. Gleerups. Lund 1970.

39. Hagberg, B. Neurologisk diagnostik i nyfödslbetsperioden, Svenska Läkartidningen, 32: 2322, 1964.

40. Hellström, B. & Jonsson, B. Late prognosis in asphyxia neonatorum. Acta Paediat Scand, 42 398, 1953.

41, Hughes, J G.: Early detection of cerebral injury J Pediat, 40: 606. 1952.

42. Illingworth, R. S. Crying in infants and children. Brit Med J, 1 75, 1955.

43. Illingworth, R. S. The Development of the Infant and Young Child. Normal and Abnormal. Fourth Ed. E & Livingstone, Edinburgh-London 1970.

44. Irwin, O. C. Research on speech sounds for the first six months of life. Psychol Bull, 38 277 1941.

45. Irwin, O C. Reliability of infant speech sound data. J Speech Dis 10 227 1945.

46. Irwin, O. C. & Chen, H. P A reliability study of speech sounds observed in the crying of newborn infants. Child Develop, 12 351, 1941

47 Irwin, O. C. & Chen, H. P Speech sound elements during the first year of life. J Speech Dis, 8 109 1943.

48. Irwin, O C. & Chen, H. P Development of speech during infancy J Exp Psychol, 36 431, 1946.

49. Irwin, O. C. & Chen, H. P Development of speech during infancy J Exp Psychol, 37 187 1947

50. Irwin, O. C. & Curry T Vowel elements in the crying vocalizations of infants under ten days of age. Child Develop 12 99 1941

51 Irwin, O C. & Curry T Vowel elements in the crying vocalizations of infants. Child Develop, 12 351, 1941.

52. Joos, M. Acoustic Phonetics. Language Monographs, 23 1, 1948

53. Joppich, G. Über zerebrale Aktivitäten bei Neugeborenen und jungen Säuglingen. Deutsch Med Wschr, 50 2296, 1967

54. Joppich, G. & Schulte, F J. Neurologie des Neugeborenen. Springer Verlag. Berlin-Heidelberg-New York 1968.

55. Karelitz, S., Karelitz, R. & Rosenfeld L. Infants vocalizations and their significance. In Bowman, P & Mautner H. (Ed). Mental retardation, Proc. First International Medical Conf. Grune & Stratton. New York 1960.

56. Karelitz, S. Infant vocalization, Part I, the infant cry from birth to two years of age. Phonograph Record CL 2669 A. 1962.

57 Karelitz, S. & Fisichelli, V R. The cry thresholds of normal infants and those with brain damage. J Pediat, 61 679, 1962.

58. Karelitz, S., Fisichelli, V R., Costa, J Karelitz, R. & Rosenfeld, L. Relation of crying activity in early infancy to speech and intellectual development at age three years. Child Develop, 35 769, 1964.

59. Karelitz, S., Fisichelli, V R., D is, J. & Haber, A. The role of crying activity in Apgar Scoring. Intercomparisons among the signs of the Apgar scale. JAMA, 198 318, 1966.

60. King, H. L. & Bourgeois, G. A. Vagitus uterinus. Bull U S Army Med Dep 7 147 1947

61. Koivisto, M., Wasz Hockert O., Vuorenkoski, V Partanen, T & Lind, J. Cry studies in neonatal hyperbilirubinemia. Proc. XVIth Scand. Ped. Congr Suppl. 206 26, 1970.

62. Kubli, F & Berg, D The early diagnosis of foetal distress. J Obstr Gynec, 1 507 1968.

63. Kytta, J. Finnish oesophageal speech after laryngectomy sound spectrographic and cineradiographic studies. Acta Otolaryng, Suppl. 195, 1964.

64. Landtman, B., Wasz Hockert O. & Vuorenkoski, V The use of sound spectrography in pediatric cardiology Ann Paediat Fenn, 10 122, 1964.

65. Lewis, M. M. Infant speech. A stud of the beginning of language. Harcourt Brace, New York 1936.

66. Lind, J. (Ed) Newborn Infant Cry Acta Paediat Scand, Suppl. 163, 1965.

67 Lind, J Vuorenkoski, V Rosberg, G Partanen, T & Wasz-Hockert O. Spectrographic analysis of vocal responce to pain stimuli in infants with Down syndrome. Develop Med Child Neurol, 12 478, 1970.

68. Lind, J., Wasz-Hockert O., Rosberg, G., Theorell, K., Valanne, E., Partanen, T & Vuorenkoski, V Sound spectrography in pediatric diagnosis Acta Paediat Scand, Suppl. 177 113, 1968.

69. Lind, J., Wasz-Hockert O., Vuorenkoski, V Partanen, T J., Theorell, K. & Valanne, E. Vocal response to painful stimuli in newborn and young infant. Ann Paediat Fenn, 12 55, 1966.

70. Lind, J., Wasz Hockert O Vuorenkoski, V & Valanne, E. The vocalization of newborn, braindamaged child. Ann Paediat Fenn, 11 32, 1965.

71. Long, E. C. & Hull, W E. Respiratory volume flow in the crying newborn infant. Pediatrics, 27 373, 1961.

72. Lucheninger, H., Dubois, C., Vassella, F Joss, E., Gloor, R. & Wiedmann, U Spektralanalyse des

"Miauens" bei Cri-du-Chat Syndrom. Folia Phoniat. 19:27 1967.

73. Lynip A. W.: The use of magnetic devices in the collection and analysis of the preverbal utterances of an infant. Genet Psychol Monogr, 44: 221, 1951.

74. Malmberg, B.: Phonetics. Dover Publ Inc. New York 1963.

75. Massengill, R. M.: Cry characteristics in cleft palate neonates. J Acoust Soc Amer, 45: 782, 1969.

76. Massengill, R., Quinn, G. W. & Bryson, M. R.: Judging on cleft palate and normal neonatal cries. Percept Motor Skills, 22: 963, 1966.

77. McCarthy D. Organismic interpretation of infant vocalizations. Child Develop, 23: 272, 1952.

78. Michelsson, K., Vuorenkoski, V., Partanen, T. & Valanne, E., Wasz-Höckert, O. Identifikation av spädbarnets preverbala kommunikation. Finska Läkaresällsk Handl, 43 109, 1965.

79. Miller, G. A. Language and Communication. Mc Graw-Hill. New York 1951.

80. Minnigerode, B. Klinische und Vergleichend-anatomische Untersuchungen zur Erzeugung der hohen Schrilltöne menschlicher Säuglinge. Arch Ohrennasw Heilk. 181 208, 1963.

81. Nelson, W. E.: Textbook of Pediatrics. 8th Ed. W.B. Saunders Co. Philadelphia-London 1964

82. Novak, A. Akustická analyza klasu deti se syndromem Downovym. Cesk Otolar, 16 26, 1967

83. van Oordt H. W. A. & Drost H. A. Development of the frequency range of the voice in children. Folia Phoniat, 15 289, 1963.

84. Ostwald, P. F. Soundmaking. The acoustic communication of emotion. C. C. Thomas, Springfield, Ill. 1963.

85. Ostwald, P. F. Freedman, D. G. & Kurtz, J. H. Vocalization of infant twins. Folia Phoniat, 14 37 1962.

86. Ostwald, P. Peltzman, P. Greenberg, M. & Meyer, J. Cries of trisomy 13—15 infant. Develop Med Child Neurol, 12 472, 1970.

87. Ostwald, P. F. Phibbs, R. Y. Fox, S.: Diagnostic use of infant cry. Biol. Neonat, 13 68, 1968.

88. Palva, T. Whispered voice audiometry. Acta Otolaryng, 49 531, 1958.

89. Parmelee, A. H. Infant speech development. Report of the study of one child by magnetic tape recordings. J Pediat, 46 44 1955

90. Parmelee, A. H. L. crying and neurologic diagnosis. J Pediat, 1 96.

91. Partanen, T. J., Wasz-Höckert, O., Vuorenkoski, V., Theorell, K., Valanne, E. H. & Lind, J. Auditory identification of pain signals of young infants in pathological conditions and its sound spectrographic basis. Ann Paed Fenn, 56 196

92. Partiainen, S. Vagitus uterinus. Ann Chir Gyn Fenn, 3 330, 1948.

93. Penrose, L. S., Smith, G. F.: Down Anomaly. J. A. Churchill. London 1966.

94. Potter, R., Kopp G. A. & Green, H. C.: Visible Speech. Van Nostrand. New York 1947

95. Prechtl, H. & Beintema, D.: The neurological Examination of the Full-term Newborn Infant. The Spastics Society Medical Education and Information Unit/William Heinemann Medical Books. London 1964.

96. Rheingold, H. L., Gewirtz, J. L. & Ross, H. W.: Social conditioning of vocalizations in the infant. J Comp Physiol Psychol, 52: 68, 1959

97. Ringel, R. L. & Kluppel, D. D.: Neonatal crying: A normative study. Folia Phoniat, 16 11, 1964.

98. van Riper, C.: Speech Correction Principles and Methods Prentice-Hall. New Jersey 1954.

99. Rudolph, A. J. Desmond, M. M. & Pineda, R. G.: Clinical diagnosis of respiratory difficulty in the newborn. Ped Clin N Amer, 13 669 1966.

100. Sedláčková, E. Analyse acoustique de la voix de nouveau-nés. Folia Phoniat, 16: 44, 1964.

101. Sedláčková, E. Composition acoustique des manifestations vocales des enfants dans la période de lallation. Folia Phoniat, 19: 351 1967

102. Schaffer, A. J. Diseases of the Newborn. Sec. Ed. W.B. Saunders Co Philadelphia-London 1965.

103. Sherman, M.: The differentiation of emotional responses in infants. J Comp Psychol, 7 335, 1927

104. Thoms, L. Cerebral symptoms in the newborn. Acta Paediat Scand, Suppl. 195, 1969.

105. Towell, M. E. The influence of labor on fetus and the newborn. Ped Clin N Amer, 13 575, 1965.

106. Truby H. M. Some aspects of acoustical and cineradiographic analysis of newborn-infant and adult phonation and associated vocal tract activity. J Acoust Soc Am, 32 1518, 1960.

107. Valanne, E. H., Vuorenkoski, V. Partanen, T. J., Lind, J. & Wasz-Höckert, O., The ability of human mothers to identify the hunger cry of their own infants during the lying-in period. Experientia, 23: 768, 1967

108. Vulliamy D. G. The Newborn Child, Churchill. London 1961.

109. Vuorenkoski, V. Kaunisto, M., Tjernlund, P. & Vesa, L.: Cry detector. A clinical apparatus for surveillance of pitch and activity in the crying of a newborn infant. Acta Paediat Scand, Suppl. 206:103, 1970.

110. Vuorenkoski, V. Lind, J., Partanen, T. J., Lejeune, J., Lafourcade, J. & Wasz-Höckert, O. Spectrographic analysis of cries from children with Maladie du Cri du Chat. Ann Paediat Fenn, 12 174, 1966.

111. Vuorenkoski, V. Lind, J. & Wasz-Höckert O. La reacción maternal al llanto del recién nacido. XII Intern Congr Ped. Mexico 1968.

112. Vuorenkoski, V Lind, J Wasz-Höckert, O. & Partanen, T J. Cry score. A method for evaluating the degree of abnormality in the pain cry response of the newborn and young infant. QPSR, in print.

113. Vuorenkoski, V Wasz-Höckert O., Koivisto, E. & Lind, J.: The effect of cry stimulus on the temperature of the lactating breast primipara. Experientia, 25 1286, 1969.

114. Wasz-Höckert, O., Koivisto, M., Vuorenkoski, V Partanen, T J. & Lind, J. Spectrographic analysis of pain cry in hyperbilirubinemia. Biol neonat, 17 260, 1971.

115. Wasz-Höckert O., Lind, J., Vuorenkoski, V Partanen, T & Valanne, E.: The Infant Cry A Spectrographic and Auditory Analysis. Clin Develop Med No 29. Spastics Internat Med Publ/William Heinemann Med Books 1968. *In spanish version* 1970.

116. Wasz-Höckert O., Partanen, T J., Vuorenkoski, V Valanne, E. & Michelsson, K. The identification of some specific meanings in newborn and infant vocalization. Experientia, 20 154, 1964.

117 Wasz-Höckert, O Partanen, T Vuorenkoski, V Valanne, E., Michelsson, K.: Effect of training on ability to identify preverbal ocalizations. Develop Med Child Neurol, 6 393, 1964.

118. Wasz Höckert O Sedláček, S., Rosberg, G., Vuorenkoski, V Lind, J.: El síndrome de Smith-Lemli-Opitz en dos niños con especial atención los patrones de sus gritos de dolor. Rev Mex Pediat, 38. 63, 1969.

119. Wasz-Hockert, O., Vala e, E., Vuorenkoski, V Michelsson, K., So mlaivi, A. Analysis of some types of ocalization in the newborn and in early infancy Ann Paediat Fenn, 9: 1 1963.

120. Wasz-Hockert O., Vuoren oski, V Valanne, E. & Michelsson, K.: Tonspectrographische Untersuchungen des Säuglingsgeschreis. Experientia, 18 583, 1962.

121. Wasz Hockert O., Vuorenkoski, V Valanne, E., Michelsson, K. & Lind, J Estudios espectrográficos de los gritos de hambre en los recién nacidos infantes. Rev Mex Pediat, 33 98, 1964.

122. Watson, E. H. & Lowrey G. H. Growth and Development of Children. Year Book Publs. 1951.

123. Weinberg, Sound Diagnoses. Phonograph record. 1970.

124. Wolff, H. Spectrographic investigation of infant cries. J Genet Psychol, 96. 171, 1960.

125. Wessel, M. A. Paroxysmal fussing in infancy Pediatrics ,14 421, 1954.

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

150. Moe, Peter Johan, Iron Requirements in Infancy. Longitudinal studies of iron requirements during the first year of life. Sw. kr. 25.— 1963
151. *Preventive Paediatrics in the Undergraduate Curriculum. Symposium Held with the Collaboration of the World Health Organization of the X International Congress of Paediatrics, Lisbon, 1962.* Edited by Bo Vahlquist. Sw. kr. 15.— 1963
152. Hjern, Bo and Nylander, Ingvar. Acute Head Injuries in Children. Traumatology, Therapy and Prognosis. Sw. kr. 15.— 1964
153. Thorén, Claes, Cardiomyopathy in Friedreich's Ataxia. With Studies of Cardiovascular and Respiratory Function. Sw. kr. 25.— 1964
154. Hall, Bertil, Mongolism in Newborns. A Clinical and Cytogenetic Study. Sw. kr. 30.— 1964
155. Engström, Inga, Respiratory Studies in Children. XI. Mechanics of Breathing, Lung Volumes and Ventilatory Capacity in Asthmatic Children from Attack to Symptom-free Status. Sw. kr. 25.— 1964
156. *Nils Rosén von Rosenstein and his Textbook on Paediatrics.* Edited by Bo Vahlquist and Arvid Wallgren. Sw. kr. 25.— 1964
157. Brante, G., Kaijser, K. and Öckerman, P. A., Glycogenosis Type I (Lack of Glucose-6-Phosphatase) in Four Siblings. Sw. kr. 15.— 1964
158. Aarskog, Dagfinn, Cortisol in the Newborn Infant. Sw. kr. 25.— 1965
159. *Proceedings of the Fourteenth Northern Paediatric Congress,* Stockholm 1964. Edited by Y. Larsson. Sw. kr. 25.— 1965
160. Öckerman, P. A., Glycogen Storage Disease in Sweden. Sw. kr. 25.— 1965
161. Peltonen, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis. A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children. A Longitudinal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margot, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 30.— 1966
172. *[illegible] in Memory of Constantin [illegible].* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Oesophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Ove, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. [illegible], Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress,* Bergen. 1967. Sw. kr. 35.— 1967
178. [illegible], *Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size.* Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children with Urinary Tract Infection, Using the Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Gunter, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alv F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. [illegible], The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, [illegible], Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1969
188. Meeuwisse, Gerard W. and Melin, Karin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. [illegible], Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. [illegible], Antti, Studies on the Serum Binding of Vitamin B12 in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 25.— 1969
196. [illegible], Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969
197. [illegible], Pseudomonas Infections in a Pediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. [illegible], Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Sanjur, Diva M., Cravioto, Joaquín, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 25.— 1970
201. Sutherland, Lynette E., [illegible], Phyllis, [illegible], John G., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatus and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N. and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kerstin, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress,* Turku, August [illegible]–August 3, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 25.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Lund. Sw. kr. 35.— 1970
210. [illegible], Parental Attitudes to Pediatric Hospital Admission. Sw. kr. 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. [illegible], Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971
214. Samuelson, Göran, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 25.— 1971
215. [illegible], A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr. 25.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971

Price Swed. kr. 25.—

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 218 1971

THE EFFECT OF A NORTHERN CLIMATE ON SEASONALITY OF BIRTHS AND THE OUTCOME OF PREGNANCIES

BY PAULA RANTAKALLIO

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 218 1971

THE EFFECT OF A NORTHERN CLIMATE ON SEASONALITY OF BIRTHS AND THE OUTCOME OF PREGNANCIES

BY PAULA RANTAKALLIO

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

Printed in Finland
KIRJAPAINO OSAKEYHTIÖ KALEVA
Oulu 1971

Contents

INTRODUCTION 5

PURPOSES OF THE PRESENT STUDY 6

REVIEW OF THE LITERATURE 7

MATERIAL AND METHODS 12

1. The study area 12
2. The climate of the study area 12
3. The recording of climatic determinants for study purposes 12
4. The climate in the study period 13
5. The study population 15
) General considerations 15
   b) Some biological and socio-economic characteristics of the study parturients 15
6. Methods 16
) Time of conception and organogenesis 16
   b) Computing the influence of climatic factors 17
) Denoting the significances 17
   d) Computing and using the percentile values 17
) Discriminant function analyses 17

RESULTS 18

1. Seasonal variations in rate of births, expected dates and conceptions 18
) Total series 18
   b) Social classes 19
) Parity 19
   d) Marriage 19
) Risk groups 21
2. Seasonal variations in birth weight 26
) By seasons only 26
   b) Variations in birth weight by temperature 27
) Seasonal variation in birth weight by sex 28
   d) Seasonal variation in birth weight by social class 28
3. Seasonal variation in boy-girl ratio 29
4. The effect of individual climatic factors at the time of delivery 29
) *The differences in mean values for climatic factors in risk groups and control groups* 29
   b) The influence of extreme values for temperature and depth of snow cover 33
5. Social, economic and biological factors operating parallel with the climatic factors 35
) The origin of the members of the cold and warm groups in different parts of the study area. 36
   b) The nature of place of residence of members in the cold and warm groups 36
) Differences in the level of housing between the cold and warm groups 37
   d) Differences in the social status between the members of the cold and warm groups 38
) Working conditions of the members of the cold and warm groups 39

f) State of health and health care in the cold and warm groups 39
g) Biological characteristics of mothers in the cold and warm groups 40
h) The pregnancy outcome in the cold and warm groups 42
) Discriminant function analyses 43
6. The influence of the climatic factors on conception and organogenesis 44
) Conception 45
b) Period of organogenesis 45

DISCUSSION 47

1. Material and method 47
a) Climate of the study area 47
b) Population of the study area 47
c) Method 47
2. Seasonal variations in rate of expected dates, births and conceptions 48
3. Seasonal variations in birth weight 51
4 The seasonal variation in boy-girl ratio 52
5. The influence of different climatic factors 52
6. Social, economic and biological factors operating parallel with the climatic factors 53
7 The result of discriminant function analyses 55
8 The pregnancy outcome in the extreme temperature groups in winter 56
9 The effect of climate on conception and organogenesis 56
10. General discussion 57

SUMMARY 59

ACKNOWLEDGEMENTS 62

REFERENCES 63

APPENDIX 65

Table 40 Monthly variations in births, expected dates and conceptions 65
Table 41 Monthly ariations in births by social classes 65
Table 42 Monthly variations in conceptions for primiparas 66
Table 43 Monthly variations in births and expected dates for perinatal deaths 66
Table 44 Monthly variations in births and expected dates for preterm infants 67
Table 45 Monthly variations in births and expected dates for postterm infants 67
Table 46 Monthly variations in births and expected dates for low birth weight infants 67

Introduction

The success of a pregnancy is judged by the characteristics of the outcome, the baby and the most important features are the intrauterine growth and development of the child that is born and the duration of the pregnancy Fertility is in practice measured by the number of the children born. The determinants affecting these characteristics are gene action on the one hand and environmental factors on the other

Climatic factors no doubt belong among the environmental factors which determine fertility and the outcome of pregnancy Even if the literature is not very comprehensive in this specific field, the correlation between health and climate was remarked upon long ago Hippocrates states «whoever wishes to investigate medicine properly should proceed thus, consider the seasons of the year and what effect each of them produces. Then, the winds, the hot and the cold, and then such as are peculiar to each locality (20)

There is no doubt that the effects of the climatic factors depend in many ways on the biological characteristics, the social behaviour and the economic standing of the population studied. Therefore it is possible to study the effect of climatic factors on human beings only in the population about which many other factors are also known. This is the case regarding the population in the present study

A detailed prospective study concerning the biological characteristics and social and economic standing of the parturient population in Northern Finland in 1966 had been started in autumn 1965 (44). The winter of 1965—66 happened to be a very cold one, only twice or three times over a period of a hundred years is the winter that cold in the area. This awakened my interest in studying the influence of a northern climate on seasonality of births and outcome of pregnancies, that is, perinatal mortality low birth weight and prematurity

The purposes of the present study

1) To examine the seasonal variations in birth and conception rates in the total series and separately for the various socio-economic and parity groups.

2) To examine the seasonal variations in birth weights.

3) To find out what effects climatic factors (temperature, relative humidity duration of daylight and snow depth) during pregnancy and on the day of birth have

a) on the rate of preterm births
b) on the rate of perinatal mortality
c) on the rate of low birth weight infants.

4) To correlate the biological characteristics and the social behaviour and economic standing of the mother with the findings.

Physiological reactions as a result of a northern type of meteorological stimulation

Andersen *et al* (1 2, 66—68) studied the question of whether physical training induces a physiological adjustment so that tolerance of cold increases and whether the exposure to cold has any physiological effects other than those induced by physical training. 19 young men were subjected to vigorous physical training for 5 weeks and half of them were also exposed to cold conditions. The results for the total group were 1) the mean maximum oxygen intake increases. 2) After the period of physical training the resting metabolic rate was higher than before. 3) The physical training and exposure to cold did not lead to a shift from shivering to non-shivering thermogenesis. The physical training led to better sleep in exposure to cold. 4) The average skin surface temperature tended to be higher after the period of physical training. 5) The training period induced a thyroid response indicated by the higher $PB^{131}I$ values. 6) There was no indication of long term stimulation of the pituitary adrenal axis as an effect of continued exposure to cold and/or increased activity After exposure to cold, however significantly higher corticosteroid values were observed. These were interpreted as a short term effect of acute exposure to cold and were attributed to the change in plasma water content and not as evidence of increased adrenocortical activity There was no significant difference between the group with physical training only and the group with physical training and exposure to cold. The possible stimulation of the hypothalamus-pituitary axis as a result of the training system is discussed. The authors suggest that their work supports the view that the differences observed between the ethnic groups in their physiological responses to cold may be unrelated to cold acclimatisation and may be explained by greater habitual physical activity

Rai (42) studied the oxygen consumption, shivering and skin and rectal temperature of natives in a standard exposure to cold at high altitudes and also in a group staying there 11 months and in a group of subjects taken there. The cold induced oxygen consumption and shivering rate were significantly lower in the natives. No significant difference was found in the body temperature in the three groups.

The influence of various meteorological stress conditions on the physiological reactions of animals has been studied in several works. Reference may be made here to a general survey on the meteorological factors contributing to physiological reactions (7).

Seasonal variation in births

The National Center of Health Statistics in the United States has investigated the seasonal variation in births in the United States of America over the thirty year period from 1933 to 1963 (64) There was an average seasonal difference of about 15 per cent between the peak month September and the months with fewest births, April

and May For four months of the year July to October the number of births was above the monthly average. This distribution of births in the United States has shown no major changes in its modal points since 1933 and seasonal fluctuations over the past 31 years have tended to increase rather than decrease. The distribution of non-white births by months shows greater variation than that of white births. The monthly fluctuation in births was greatest in the Southern states and least in the North-Eastern states. The seasonal variation in births did not appear to be related to the time of marriage, the age of the mother nor order of the child, but it was not possible to exclude the correlation of the socio-economic status of the parents and climate with the season of the births (64)

Pasamanick *et al* (36—37) has also been interested in the seasonal variations in American births. He suggests several factors as reasons for the monthly disparities. One is the high summer temperature and humidity the discomfort it causes reduces sexual activity and adversely affects the viability of sperm, the latter meaning that there is an increased foetal death rate among conceptions occurring in the summer months.) The authors also found that the seasonality varied inversely with the socio-economic data (37). They think that a higher socio-economic group is better able to modify the effects of the climate by air conditioning. The higher socio-economic group also has better nutritional habits and is therefore able to minimize dietary deficiencies that might affect foetal mortality Higher socio-economic status also makes it possible to utilize birth control effectively by family planning practices (37

Zelnick (70) on the other hand, also using the American data in a study on the socio-economic influences on seasonal variations in births from 1961 to 1965 found that the highest and lowest socio-economic groups were not different or differed only by chance. He also disagrees with the opinion that the greater ability of the upper socio-economic status group to modify the effects of climate, to practice better nutritional habits and to utilize birth control devices more efficiently would necessarily lead to a uniform monthly distribution of births he thinks that all this could just as easily lead to an increasing amount of monthly variability He himself points out the possible importance of holidays and customary vacation practices in the timing of births.

Chang *et al* (5) found in their stuby a high negative correlation between the temperature and conception rate ($r = -0.97$) in Hong Kong concerning births in the period of 1951—1961 A clear peak for conception rates is in winter and a depression in summer from May to September The summer conception rates were about 30 per cent lower than winter The correlation between conception rates and temperature was the same for urban and rural areas and for different parity groups. The air pressure, air movement and rainfall also showed some correlation with the conception rates, the correlation being positive for the first two and negative for the rainfall.

The international figures for the seasonal distribution of births show an interesting bimodal pattern for many countries with a constant minor and major peak (64) For England and Wales, Sweden and West Germany the minor peak occurs in September The major peak in Sweden is a very high one in April and In West Germany and in England and Wales the distribution curves are very similar having the major peak clearly flatter than in Sweden, lasting in the former country from February to May and in the latter from March to May

In Finland the old figures for the distribution of birth rates from 1904—09 1924—29 and 1934—39 show peak values in July and

lowest values in October (28). When the figures for the earlier years, 1904—09 were compared with the figures for the years 1934—39 it was seen that the annual fluc tuation was flatter in the latter series. When the birth rates in rural and urban areas were examined separately the distribution in rural areas was about the same as in the total series, but for the urban population the highest birth rates were from March to July As an etiologic cause of the maximum birth rate in July and the corresponding maximum conception rate in October the authors suggest, in the first place, the fact that after the summer the general health and nutritional state of the population is at its maximum. To support this hypothesis they point to the diminution of the fluctuation in birth rates during a 30 year period parallel to the improvements in nutrition. The authors also discuss the possible effect of the duration of daylight on conception activity

Timonen *et al* (58) have studied in their work the distribution of birth rates in Helsinki district during the period of 1956—60 and found a highly significant correlation by regression analysis between the number of sunshine hours and conceptions but not between the temperature and the number of conceptions. The authors interpret the results as indicating the stimulatory effect of light on the LH production of the pituita ry

Effects of seasons on birth weight

Marshall (29) has collected data concerning the seasonal variation in birth weight from literature. Most of the authors had not found any difference between the seasons but when found, the season with maximum birth weight varied from winter to summer and included spring and autumn

The more recent literature concerning the seasonal fluctuation in birth weights mainly deals with the southern regions. In the Singapore series (32) the average birth weight of infants was not significantly different from one month to another nor from the mean for the year Ramaiah and Narasimham (43) in their Indian sample found that the mean birth weights were highest in the summer months, March-June, and the difference between the means for summer and winter was significant. The summer winter difference in birth weights was found in all parity groups but in different social classes only in the lowest one whereas in the upper classes the mean birth weight was not dependent on season. Sarkar (50) in his South Indian series found the highest mean for birth weight in March and the lowest in December The author suggests that the better intake in both quantity and quality of food by the expectant mother may be the reason for the heaviest birth weight falling in the late winter-spring period.

The influence of seasons on births of mentally deficient children and on congenital anomalies of the central nervous system

Knobloch and Pasamanick have been inter ested in their work in the connection between the births of mentally deficient children and the season of the year (25—27). In their study they found that the incidence of births of mentally defective children in Ohio, USA, was significantly higher in the winter months of Janyary February and March. They think that the etiological factors are to be found in the third month after conception when the cerebral cortex of the unborn child is becoming organized. The months when this might happen concerning the children born in winter would be June, July and August. The authors think that the hot weather decreases the food intake of mothers, par

ticularly protein, and that it damages the developing foetuses.

Perlstein and Hood have studied in their work the seasonal variation in congenital cerebral palsy in the Northern part of the United States (39) The incidence was proportionally highest in summer and spring. The authors thought the later part of pregnancy to be the period when the deleterious effects were operating on the foetus and therefore found the late winter and spring to be the seasons causing the increased incidence of cerebral palsy in spring and summer The damaging factors in the spring weather could be its variability and the sudden rises of the temperature.

McKeown and Record (30) found in their study that the incidence of infants with anencephalus was significantly higher a mong children born in the half-year from October to March than among those born in the half year from April to September in the series collected in Scotland and Birmingham. The authors thought that the findings could give rise to the suggestion that the higher incidence of anencephalus in winter is related to the seasonal incidense of infectious diseases, but they failed to find the positive history of specific fevers during the mothers [illegible]y The authors did not find any [illegible] variation in the incidence of spina [illegible] or hydrocephalus.

Edward (9) also found that there was a marked seasonal variation in the incidence of anencephalus but not of spina bifida or hydrocephalus, the peak incidence in this Scottish series falling between late October and late February every winter over a period of 18 years. The author presumes, however that the climate itself is of less importance as an etiologic factor of the anomalies and suggests that other environmental influences have a greater importance

Record has further studied the incidence of anencephalus in Scotland (46) The highest incidence was found among infants born in the November January period. The probable time for the initiating of the malformation was found to be from March to July There was no evidence that infectious diseases were more frequent during that season but daylight and sunshine gave a closer correspondence.

Gutkelch (18) re-examined the work of McKeown and Record (30) and found the rate of spina bifida stillbirths in this study to be higher in each month between December and May than in any of the remaining months of the year a finding which the original authors had failed to observe. In his own series from Manchester he also found a considerable excess of spina bifida births in the period from December to May

Collmann and Stoller (6) studied the seasonal variation in mongoloid births. They confirmed that there were no significant differences in the incidence of births of mongoloid children between the various months and quarters of the year

Seasonality of perinatal mortality

Eastman (10) in his study based on the Annual Reports of Births in the United States investigates the perinatal mortality among children born from 1935 to 1937 Both the stillbirth and neonatal mortality rates were found to be higher in winter months than in summer Also prematurity was more frequent in winter The cause of the increased incidence of stillbirths in winter was thought to be the weather conditions which at that time of the year seriously impair the health of the expectant mother The causes of the increased number of neonatal deaths in winter were thought to be the increased prematurity rate and frequent infectious diseases in winter

In the national statistics of the United States concerning the year 1950 (62) seasonal differences were also found both in the

incidence of premature births and neonatal mortality However the proportion of premature children in the first three months was slightly smaller than in the year as a whole. The neonatal mortality was also lower among the children in the period from January to March. The differences were small but statistically significant. The basis for the lower neonatal mortality was thought to be the lower rate of premature births.

In the study of perinatal mortality in Scotland in the years 1961—63 (63) it was found that the season of the year has no effect on the probability of a pregnancy resulting in a stillbirth.

Material and methods

1 The study area

The study area covers the most northern part of Finland, the provinces of Oulu and Lapland (Fig 1) The area forms about 48 per cent of the total area of Finland and covers 160 000 sq.km. The district is situated at 63 30 — 70°00 North and 21°00' — 30 31 East. The arctic circle is situated in the middle of the area. The border line between the province of Lapland and the province of Oulu runs some seventy five kilometres below the arctic circle so that each province includes three of the registration centres indicated in Fig. 1

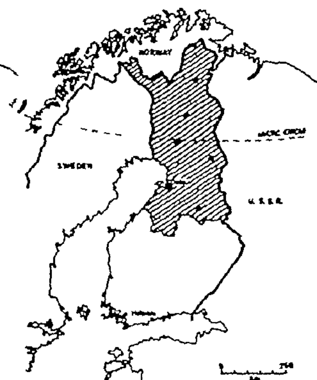


Figure 1 The study area. The six observation centres where the climatic data was gathered are indicated.

2. The climate of the study area

In the South—West part of the area the climate is maritime and it changes to continental in the eastern part. January is the coldest month when the mean temperature on the average is —12 C. The warmest month is July with the average mean temperature of +15 C. Figure 2 shows the variations in the mean day temperature during the year The figures for temperatures are means calculated from over a period of 30 years. The temperature values for the most southerly and the most northerly parts of the area are shown in the Figure. The differences in the mean monthly temperature between the coastal area and the most southerly inland part as 3°C in December and January the temperature on the coast being higher and in the other months of the year the differences in temperature means are less than 1 C. Daylight in December averages 2 hours and in June 23 hours per day The maximum difference in the duration of daylight between the most northerly and the most southerly parts of the study area is about 5 hours. From the end of March until the end of September the day is longer in the North

3 The recording of climatic determinants for study purposes

The data concerning the climatic factors were collected in the six different centres seen in Figure 1 by the Finnish Meteorological Institute as part of a general registration program, independently of the present

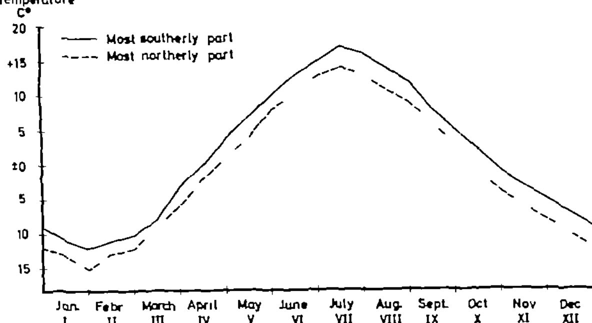


Figure 2. The monthly variations in the mean temperature values from over period f 30 years in the most southerly and the most northerly part f the study area.

study project. The centres were chosen for the study as being repsentative of the climate of the surrounding area. Recordings were made for each individual day on which the study was undertaken. According to their place of residence, each individual mother and child had the climatic values recorded at the nearest representative centre.

The population is not equally distributed over the study area. The size of the study population belonging to each climatic obser vation centre is as follows, when the places marked in Figure 1 are taken from the North to the South:

Ivalo	192 births
Sodankyla	681
Ro aniemi	2,804
Kuusamo	1,062
Oulu	4,655
Kajaani	2,537
Total	11,931 births

For the purpose of the study the year was divided into three seasons, summer spring and autumn combined, and winter The sum mer months are June, July and August, the spring consists of April and May and the autumn September and October and the win- ter November December January February and March. This classification represents the different seasons of the year in Northern Finland in the best possible way The great est bias of this classification is the differ ence in the humidity of the spring and the autumn, the former period being relatively dry—mean relative humidity 67 % — and the latter humid-mean value being 85 %. Accord ing to th s classification the seasons do not have the same duration. Therefore, for some comparisons three months have been regarded as the winter period, namely December January and February and the winter is then called «deepest winter

4 The climate in the study period

The study population consists of all mothers in the area whose expected date was in 1966.

Normal pregnancy lasts 266 days. Thus in addition to the year 1966 the study also covers the year 1965 from the beginning of April and, concerning some babies born after their expected dates, January 1967 In 1965 from April to October the monthly mean temperature fluctuated from the long term monthly average maximally 3 centigrades. The severe winter began in November both of the last months of the year having the mean temperature from 4.5 to 7°C lower than the long term mean. In 1966 the mean temperature in January and February was from 6 to 11°C below the long term mean. In February 1966 lower temperature values were recorded in many places than ever before in the area. The lowest value was —48.6°C in Ivalo, the most northerly place and the lowest value in the most southerly area, Kajaani, was —42.8°C. March 1966 was from 3 to 8°C colder than usual The temperature for the months of the rest of the year was within the 3°C range of the normal limits. January 1967 again was from 5 to 8°C colder than usual.

The means for the six individual climatic factors used in the study are described below by seasons of the year The mean values are calculated for the days of birth and therefore they mainly represent the year 1966

Summer	
Temperature at 20.00 hrs	+ 15 1°C
Minimum temperature	+ 9.0°C
Maximum temperatur	+ 18.4 C
Relativ humidity	65.7 /
Duration of daylight	19 4 hours
Snow depth	0.0 cm
Spring + Autumn	
Temperature at 20.00 hrs	+ 3.6°C
Minimum temperature	— 1 4 C
Maximum temperature	+ 5.8°C
Relativ humidity	74.6 /
Duration of daylight	14.5 hours
Snow depth	12.7 cm
Winter	
Temperature at 20.00 hrs	— 12.8°C
Minimum temperature	— 17.2°C
Maximum temperature	— 9.0°C
Relative humidity	83.7 %
Duration of daylight	7.2 hours
Snow depth	35.1 cm

In the following tables the 10th and 90th percentile values are given for some of the climatic factors separately for the three different seasons.

Summer	10th percentile	90th percentile
Temperature at 20.00 hrs	+ 9.3 C	+ 20.9°C
Minimum temperature	+ 3.3 C	+ 14.7°C
Relative humidity	43.2 %	68.3 %
Snow depth	0.0 cm	0.0 cm
Spring + Autumn		
Temperature at 20.00 hrs	— 4.0°C	+ 11 1 C
Minimum temperature	—10.0°C	+ 7 1°C
R lativ humidity	51.4 /	97.8 %
Snow depth	0.0 cm	38.1 cm
Winter		
Temperature at 20.00 hrs	— 25.0°C	— 0.5°C
Minimum temperature	— 31.5°C	— 2.8°C
Relativ humidity	69 9 /	97.5 %
Snow depth	6.8 cm	63.3 cm

Even if the population is not equally distributed over the study area, the climatic figures above do give a correct illustration of the climatic conditions where the study population lives, because the figures used as the basis for the mean values are taken separately for each study person.

In different parts of the large study area the seasons of the year begin and end at different times. As can be seen in Fig.2, there is some 2 weeks' difference between the most southerly and the most northerly area as to the beginning and ending of winter Therefore, in some calculations the mean value for the temperature of every particular day calculated from over a period of 30 years is used for each individual person in the same way as the actual temperature of the day In such cases, of course, the mean for the 30 year period in the first place represents the season expressed as a temperature value

The coldness of the winter and the depth of the snow cover are not exactly parallel. As is seen in Fig 2, the coldest period with the mean temperature of —10°C or below lasts from December to March. The deepest snow

depth, however usually occurs in the latter part of winter The value which was given for the 90th percentile for snow depth (I.e. 63 cm) on the birth day of the study population was not attained at all in two of the observation places, Oulu and Rovaniemi, in 1966. In the other four places that depth was first reached at the end of February

5 The study population

a) General considerations

The total population of the study area is about 604 000 inhabitants. The majority of the population is Finnish but some 3,500 Lapps live in the northernmost part of the area.

The study population comprised all the births during one year 1966.The data consernіng social, economic and biological characteristics of the mothers were collected by questionnaire in the antenatal clinics of the district. The details concerning collection of the data are given in my earlier monograph. (44) Since the study was prospective, inclusion in the survey was determined by the calculated term the series comprised all mothers in this district with calculated terms falling between Janyary 1 st – December 31 st 1966

All deliveries giving birth to a child of at least 600 grams weight were counted as a birth. *Perinatal deaths* comprised stillbirths and neonatal deaths before the age of 28 days. *Low birth weight infants* were babies with birth weights under 2500 grams.

Information is available on 11 931 single births in the district in that year (44) 7 885 births, some 66 per cent of the total, occurred in the province of Oulu and the rest, 4 046 births, in the province of Lapland. The total number included 283 *perinatal deaths* which is 95,8 per cent of the relevant mortality in 1966, and 499 *low birth weight infants* which is 97 0 per cent of the relevant 1966 figure for the district (44)

All the infants of a gestational age between the beginning of the 38th and the end of 42nd gestational week have been considered as *term births Preterm* births were taken as those born prior to the beginning of the 38th gestational week, their number totalled 1 035 births. *Postterm* means all births of a gestational age of 43 weeks or more. Their number was 636 In 395 births, the gestational age was unknown to the accuracy of the exact week, in 577 cases it was unknown to the accuracy of the exact day and in 124 births the expected calendar months were unknown. The details concerning the calculation of the expected delivery dates are described in an earlier work (44).

The birth weight was known in all cases. The recording and calculation of the children s weight have been described earlier (44) The cases of perinatal mortality low birth weight infants and preterm births are called *risk groups* in this study

b) Some biological and socio-economic characteristics of the study parturients

The age distribution of the mothers is shown in table 1 In 37 cases the age is unknown.

The parity figures of the series are shown in table 2. In 27 cases the parity is unknown.

From the total population in the district, one third, some 204 000, are urban dwellers.

Table 1 *Age distribution of the mothers*

Age in years	Number of cases	Percentage of total
Less than 20	845	7 1
20—24	3 425	28.7
25—29	3.367	28.2
30—34	2.001	16.8
35—39	1.602	13 4
40 or more	654	5.5
Not known	37	0.3
Total	11.931	100.0

Table 2. *Parity distribution of the series*

Parity I means a mother having her first child

Parity	Number of cases	Percentage of total
I	3,888	32.6
II	2,870	24.1
III	1,701	14.3
IV	1,[illegible]3	10.5
V	767	6.4
VI	459	3.8
VII	337	2.8
VIII	274	2.3
IX and more	356	3.0
Not known	27	0.2
Total	11,931	100.0

Table 3 *Father's sector of economy*

Sector of economy	Number of cases	Percentage of total
Agriculture, forestry fishing	3647	30.6
Industries (incl. electricity gas, water), crafts	1794	15.0
Building	977	8.2
Commerce	828	6.9
Transport	1134	9.5
Services (public and private)	2289	19.2
Not known	1262	10.6
Total	11 931	100.0

The distribution of the study population is the same 4 014 are urban and 7 889 rural dwellers in 28 cases the place of residence remains unknown Of the rural dwellers, ,242 live in smaller population centres and 647 39 per cent, live in remote villages.

The material is presented according to the father's sector of economy in table 3 In some ten per cent of cases this question was unanswered in the questionnaire, probably partly because the father had no fixed sector owing to the lack of skill in a profession and partly because the interviewed person was not the father but the mother Some 4 per cent of the mothers were also unmarried. As can be seen from table 3 agriculture was the major sector representing one third of the group and services and industries the next. 24.9 per cent (2,973) of the fathers were farmers 26.5 per cent of the

Table 4 *Mother's sector of economy*

Sector of economy	Number of cases	Percentage of total
Agriculture, forestry fishing	[illegible]821	[illegible]3.7
Industries (incl. electricity gas, water) crafts	266	2.2
Building	44	0.4
Commerce	1394	11.7
Transport	50	0.4
Services (public and private)	2809	23.5
No occupation	4288	35.9
Not known	257	[illegible]2
Total	11,931	100.0

Table 5 *Mother's school attendance*

School attendance	Number of cases	Percentage of total
No school or ambulatory school	198	1.7
1—4 years primary schooling	839	[illegible].0
5—8 years schooling	6806	57.1
9—14 years schooling	1348	11.3
At least 6 months of vocational schooling	2236	18.7
University education	368	3.1
Not known	257	2.2
Total	11 931	100.0

study families had cattle, poultry or pigs 23.3 per cent of the mothers took part in this kind of farming

4,563 mothers, 38.9 per cent, had been fully employed outside their homes during pregnancy In table 4 the mother's sector of economy is shown. The mother's school attendance and educational level is given in table 5 Some 3 per cent had a university level of education but on the other hand 8.8 per cent had less than five years schooling In 136 cases (1.1 per cent) the mother's school attendance was not known. In the section on results some more characteristics of the mothers will be considered.

6 Methods

a) The length of pregnancy is about 266 days and so covers in majority of cases at least a part of all the three seasons of the

year. The main interest in the present study is focused on the climatic conditions at the time of conception, organogenesis and delivery.

The most probable time of the *conception* is a fortnight after the first day of the last menstrual period. In the study I have firstly tried to trace it by taking the 13th, 14th and 15th day after the last menstrual period and examined the climatic conditions during that period. Secondly I have taken a longer period with ten days on both sides of the calculated ovulation time. The spermatogenesis for the actual conception occurs a few days before the conception. Therefore this second method of examining the conditions during the conception also covers the time of ovulation and spermatogenesis.

The *organogenesis* consists of the first trimester of pregnancy. In this study it has been taken as the following 84 days after the calculated conception. The day of the *delivery* is, of course, exact, but does not necessarily fall within the period when the anticipated factors have their effect as will be seen in part of the discussion.

b) Each of the three risk groups, perinatal deaths, low birth weight infants and preterm infants, has been compared with the corresponding control group at the time of conception, organogenesis and delivery. For comparison, the *mean values for each of the seven climatic factors were computed for the risk group and the control group by different seasons*. The computing was carried out on an IBM S 360/30 computor. The significance of differences in means was tested by the t test.

c) The *significances* were denoted in the following way:

$P < 0.05$ = * = t value at least 1.96, nearly significant
$P < 0.01$ = ** = t value at least 2.58, significant
$P < 0.001$ = *** = t value at least 3.29, highly significant

d) When indicated, *percentile* values were computed for some of the climatic factors (minimun temperature, snow depth). Percentiles are the confidence limits computed on the basis of the mean. The percentile values were used to see if the extreme values for some variable, for example temperature, gave the results of the same magnitude as suggested by the differences in mean in the groups compared.

The 10th and 90th percentiles of the minimum temperature on the day of birth in the group born in winter were also used in the following way: the total population belonging to the coldest ten per cent and the warmest ten per cent of days were taken separately and several characteristics of the mothers and their infants were compared in the groups.

For most of the variables used there was a certain percentage of unknown data. This percentage was usually less than five per cent (44). In the following the group with known data is taken as the total for each variable.

e) Discriminant function analysis was used to see how some of the climatic factors separate the risk group from the control group when used among a number of other variables. The mathematics used in discriminant functions was the same as in the earlier study (44) except that the program initially made for the Elliot 803 computer was modified so as to be suitable for the IBM S 360/30 computer.

Results

1 Seasonal variations in rate of births, expected dates and conceptions

a) Total series

In Figures 3 4 and 5 the monthly variations in births, expected dates of deliveries and estimated number of conceptions in the total series are shown. In each month an index for the number of births, expected dates and conceptions is calculated. This shows the deviation from the annual average of 100 per month after the varying numbers of days in each month have been adjusted. The number and percentage figures are shown in detail in table 40 in the Appendix.

The rate of births shows two peaks, from April to June and in August, but the rate of expected dates shows its highest peak from March to June. There is a remarkable drop in the rate of births and expected dates in February compared with the corresponding rates in the surrounding months. The peak for the rate of conceptions is from July to September Beginning from December the



Figure 4 Seasonal indexes of expected dates in the total series.



Figure 3. Seasonal indexes of births in the total series.

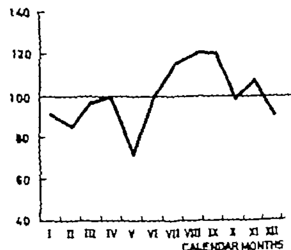


Figure 5 Seasonal indexes of conceptions in the total series.

conception figures are clearly lower in winter and spring than in the rest of the year

If we take the deepest winter from the beginning of December until the end of February we get a period of 90 days which corresponds to the duration of summer from the beginning of June up to the end of August, 92 days. The figures for the number of births, estimated dates and conceptions during those periods are as follows.

	Summer	Winter (three months)
Number of conceptions	3179	2530
Number of expected dates	3132	2458
Number of births	3327	2630

Reproductive activity during the summer months is some 25 per cent higher than during the deepest winter months.

b) Social classes

In Figure 6 the monthly variations in birth rates in different social classes are shown. Details of numbers and percentages are shown in the Appendix in table 41 The differences between social classes are not great. The differences in birth rate between the deep winter period and the summer time are smallest in social group I the rate being only some 7 per cent lower during the winter time (140 compared with 150 births). The birth rate in spring, however is high in this social group and that means that conception activity has been great in summer The difference between summer and deep winter is greatest in the lowest social group group IV 598 births in summer and 434 births in winter the former figure being some 37 per cent higher All social classes except class I show a peak in August and the farmers and social classes II + III another peak in June, but the highest peak is in April or May in all classes except the farmers whose highest peak occurs in March. The drop in February birth rates is seen in all social classes except social class IV Therefore the distribution of expected dates of February births in social class IV were examined. From the 159 cases with known month for the expected date, only 94 cases had it in February which is only 59 1 per cent of the births in that month in this social class and 4 6 per cent of all expected dates of class IV 30 1 per cent had the expected date either in March or April and 10.8 per cent in January

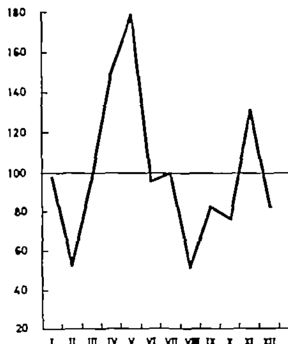
c) Parity

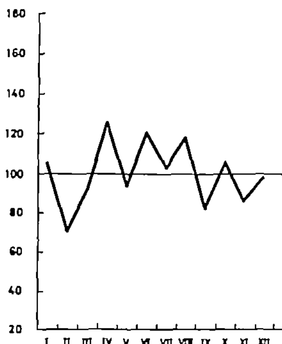
The monthly variations in conceptions in primiparas are shown in Figure 7 Details are given in the Appendix (table 42) The number of conceptions in summer 845 is only some 12 per cent higher than the figure of 755 for the deepest winter months.

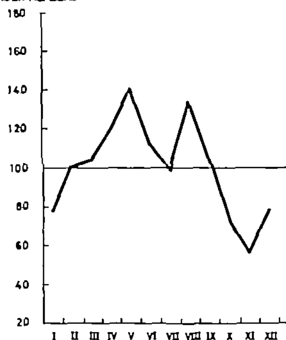
d) Marriage

The conception rate of the primiparas could be thought to b- connected with the date of marriage. In table 6 the monthly variation in marriage for the total population and separately for the primiparas is shown The favourite months are clearly seen. June, with 15 to 17 per cent of all marriages and December with some 12 per cent of the total. The least desirable months are the first three months of the year: they include some 25 per cent of the days of the year but only some 14 per cent of the marriages.

When the monthly variations in marriages and conceptions are compared, the proportionate peak of conceptions for the increased rate of marriages in June and December is not found very clearly For primiparas, therefore, the timing of the conception in relation to entering into matrimony was studied. For 3,302 primiparas both the date of marriage and the date of expected delivery were known, in 586 cases either one or other of them was unknown or the mother was unmarried. These 3,302 primiparas were grouped in the following way The first group







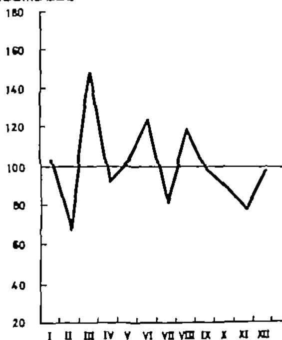


Figure 6. Seasonal indexes of birth by social classes.

Table 6 *Monthly variations in entering into matrimony for the total study population and differently for the primiparas*

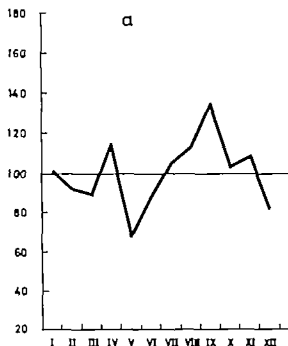
In 759 cases of the total series the date was unknown and 449 mothers were not married.

Calendar months	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Total
Total number of marriages	512	471	566	842	767	1617	1099	1008	845	863	833	1300	10.723
Percentage of total	4.8	4.4	5.3	7.9	7.1	15.1	10.2	9.4	7.9	8.0	7.8	12.1	100.0
Number of marriages of primiparas	196	110	140	263	274	579	317	336	179	344	282	396	3416
Percentage of marriages of primiparas	5.7	3.2	4.1	7.7	8.0	17.0	9.3	9.8	5.2	10.1	8.3	11.6	100.0

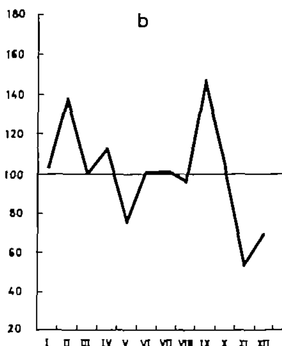
included the mothers for whom the time between marriage and th expected date was shorter than 252 days, that is more than one menstrual period shorter than the duration of normal pregnancy calculated from the first day of the last menstrual bleeding (280 days) This group comprised 1,395 mothers which is 42,3 per cent of all primiparas. The second group included mothers for whom the time between the marriage and the expected date was between 252 and 310 days, the latter figure denoting one calendar month more than the duration of normal pregnancy and this group thus included conceptions occurring around the date of entering into matrimony This group comprised 455 mothers, which is only 13.8 per cent. The next group consisted of conceptions occurring during the next two months (duration from the marriage to the expected date from 311 to 370 days) and the number here was 284 (8.6 per cent). The next group included cases with conception from the fourth to the twelfth month of marriage and the number here was 638 (19.3 per cent). The last group included the cases in which the marriage had lasted over one year before conception and the number of cases in this group was 530 which is 16.0 per cent. Thus, only 13.8 per cent of the conceptions were connected in time with the date of marriage. The total number of conceptions in the first year of marriage was thus 41.7 per cent, 16.0 occurred after the first year of marriage and 42.3 had been conceived before marriage. As can be seen from Figure 7 the distribution of conceptions for mothers whose conception had occurred before marriage did not show any summer peak, but a peak in September like the total series and the group of primiparas whose conception occured in the three first months of marriage.

e) Risk groups

The seasonal difference between births resulting in *perinatal death* and the total series is illustrated in Fig 8 For comparing the risk groups with the total series the original monthly percentage figures are used. Because of the limited number of members in the risk group, the seasonal variation is examined in the periods of two months. For January and February however the figures are also given separately The reason for that is the different share of the highest and lowest social classes of the total number of births in these two months (table 41 on page 65) which might cause the differences. When compared the corresponding figures with the total series it is clearly seen that the summer peak does not exist in the cases of perinatal deaths. On the other hand, the highest rate of births resulting in perinatal death — 18.3 per cent



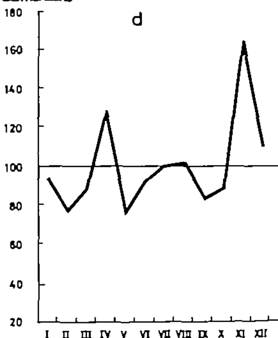
ALL PRIMIPARAS



PRIMIPARAS IN WHOM THE CONCEPTION OCCURRED BEFORE THE MARRIAGE



PRIMIPARAS IN WHOM THE CONCEPTION OCCURRED DURING THE THREE FIRST MONTHS OF THE MARRIAGE



PRIMIPARAS IN WHOM THE CONCEPTION OCCURRED AFTER THE THREE FIRST MONTHS OF THE MARRIAGE

Figure 7. Seasonal indexes of the conceptions of the primiparas, a) the total group and b—d) the sub-groups formed on the basis of the various intervals between the date of marriage and the date of conception. (The number of cases for a) is 3,302, for b) 1,395, for c) 739 and for d) 1,168)

— occurs in the November—February period compared with quite a low value — 14 4 per cent — of the total series. Table 43 in the Appendix shows in detail the seasonal variations in births and expected dates of 283 infants who died during the perinatal period. Figure 9 illustrates the seasonal differences between the expected dates in the groups of perinatal deaths and the total series.

The number of perinatal deaths for January is 30 (10.6 per cent of all deaths) and for February 21 (7.5 per cent). The rate of births in the highest social class is relatively high in January (8.3 per cent of all births in this class) and relatively low in February (4.0 per cent) and the opposite is true for the lowest class (table 41 on page 65). The increased number of deaths in this period is therefore not caused by the different proportion of births belonging to the highest and lowest social classes.

In table 7 the perinatal mortality rate for the total series per thousand during the three periods of the year is shown. It is clearly seen that *mortality is highest in winter* 29 9 per thousand compared with a rate of 18.3 per thousand in summer. The difference between these two percentage figures is statistically significant, the t value for the difference in percentages being 3.24. The difference between the perinatal mortality rate in summer and in the spring plus autumn period, 18.3 per thousand and 21.2 per thousand, is not statistically significant. The difference between the spring plus autumn period and winter 21.2 per thousand compared to 29 9 per thousand, is statistically nearly significant, the t value being 2.54

Of the 135 perinatal deaths in winter 76 were stillbirths and 59 neonatal deaths. Of the total number of 283 perinatal deaths 160 were stillbirths. The distribution into stillbirths and neonatal deaths in the winter series was thus the same as in the total series, about 56 per cent being intrauterine deaths.

The seasonal difference between birth rates of *preterm infants* and the total series is illus

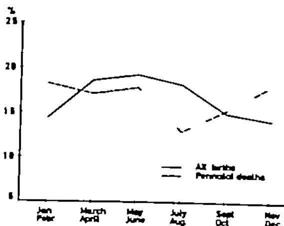


Figure 8 The seasonal variations in rates of births of perinatal deaths and the total series.

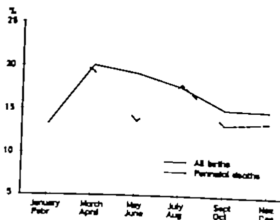


Figure 9 The seasonal variations in rates of expected dates of perinatal deaths and the total series.

Table 7 *The perinatal mortality rate per thousand in different periods of the year*

	Number of deaths	Number of all cases	Mortality per thousand
Summer	61	3325	18 3
Spring and autumn	87	4095	21 2
Winter	135	4511	29 9
All periods	283	11931	23 7

trated in Fig 10 Details are given in table 44 in the Appendix. It will be noticed that among preterm infants, too, there is a peak in births in the January February period, 19 0 per cent for preterm babies compared with the corresponding figure of 14 4 per cent for the total series.

The number of preterm births for January is 113 (10.9 per cent of all preterm births) and 84 for February (8 1 per cent) The number for the two spring months, April and May is 186 (18 0 per cent) and for the autumn months, September and October 156 (15 1 per cent)

In table 8 the incidence of preterm births in different periods of the year is shown It is lowest in summer 7 9 per cent, increases somewhat in the combined spring + autumn period, 8.3 per cent, and is highest in winter 9 6 per cent. The difference between the preterm rate in summer and in winter is statistically nearly significant, the t value for the differences in percentages being *2.57* The difference in the figures for the preterm rate between the combined spring and autumn period and winter is also nearly significant, the t value being *2.07*

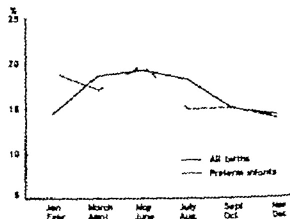
To investigate to what extent the increased mortality rate in winter is based on the increased number of premature deliveries, the seasonal variation in perinatal deaths was examined separately in the term plus postterm and preterm birth groups. The results are shown in table 9 The percentage distribution of preterm dead infants over the period from November to February is greater than the corresponding distribution of term plus postterm infants, the figures for preterm infants being 19.2 and 18.2 per cent and for term and postterm infants 16.2 and 15 4 per cent. Also perinatal deaths with unknown gestation are more numerous in winter the percentage distribution in November and December being 22.2 per cent of the total and 33.3 per cent in January February

For comparison with the preterm births the seasonal variations in *postterm births* and expected dates were also calculated. It is quite clear that the rate of postterm births differs from the total number of births in the opposite direction to the rate of preterm births the peak values are seen in the summer and autumn months and low values in winter and early spring. The results are seen in detail in table 45 in the Appendix.

The seasonal variations in births of *low birth weight infants* are illustrated in Figure 11 Here again a clear peak is seen in January February 18 9 per cent for births of low birth weight infants and 14 4

Table 8 *The incidence of preterm infants (gestation less than 38 weeks) in different periods of the year*

	Number of preterm babies	N mber of all se	Preterm babies per t
Summer	263	3325	7 9
Spring and a t m	340	4095	8 3
W nt	432	4511	9 6
All period	1035	11931	8 7



F gure 10 The seasonal variations in ates f births of preterm infants and the total series.

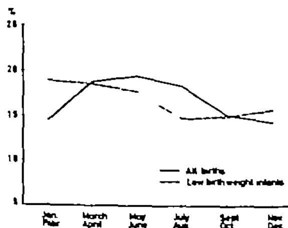


Figure 11 The seasonal variations in ates f low birth weight infants and the total series.

Table 10. *The incidence of low birth weight infants in different periods of the year*

	Number of low birth weight infant	Number of ll ases	Low birth weight infant per ent
Summe	117	3325	3 5
Spring and autumn	155	4095	3 8
Winter	227	4811	5 0
All periods	499	11831	2

for the total series respectively A flatter peak is seen in November December Details are shown in table 46 in the Appendix.

The number of low birth weight infants for January and Febryary is about the same, 48 in the former and 46 in the latter month (9.6 and 9.2 per cent of all low birth weight infants). The number for spring months is higher than in autumn months, 86 infants in April and May (17.2 per cent) and 74 infants in September and October (14 8 per cent).

The birth rate of low birth weight infants was also calculated for three periods of the year The results are shown in table 10. The incidence was lowest in summer 3.5 per cent, a little higher during the spring and autumn period, 3 8 per cent, and highest in winter 3 0 per cent, the total figure being 4.. per cent for the series. The differences in the rate of low birth weight infants between the summer and winter period and between the combined spring and autumn period and winter were both statistically significant, the t value being for the former period 3.23 and the latter 2.81

The seasonal variations in births of low

Table 9 *Monthly variations in births of infants who died during the perinatal period divided into preterm and term plus postterm infants and those whose length of gestation is unknown*

Calendar months	I+II	III+IV	V+VI	VII+VIII	IX+X	XI+XII	Total
Number of preterm perinatal deaths	27	18	29	17	28	29	148
Percentage of all preterm deaths	18.2	12.2	19.6	11.5	18.9	19.6	100.0
Number of term + postterm perinatal deaths	18	27	20	19	14	19	117
Percentage of all term + postterm deaths	15.4	23 1	17 1	16.2	12.0	16.2	100.0
Number of perinatal deaths whose length of gestation unknown	6	3	2	1	2	4	18
Percentage of all deaths w th unknown gestation	33.3	16.7	11 1	5.6	11 1	22.2	100.0
Percentage distribution of births in total series	14 4	18.7	19.3	18.3	15.0	14.3	100.0

birth weight infants were further studied by dividing the group into term and preterm babies. The results are shown in table 11. It is to be noticed that the peak in the January-February period exists for the preterm low birth weight infants, too, 19.4 per cent compared with 14.4 per cent of the total series. This finding is also shown in Fig 12. The number of term low birth weight infants is limited but they dominate the peak in the November-December period as can be seen in Fig 11 with a rate of 18.8 per cent compared with the rate of 14.3 per cent for the total series.

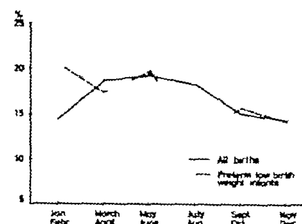


Figure 12 The seasonal variations in rates of preterm low birth weight infants and the total series.

2 Seasonal variations in birth weight

a) By seasons only

The monthly variations in birth weight means are shown in table 12. In the November-February period the means are 40 to 70 grams lower than the mean for the whole year and values clearly above the mean occur sporadically in March and May 3,504 grams and 3.517 grams. The mean birth weight for the three summer months of June-August was 3 441 grams, for the five

Table 12 *Monthly variations in birth weights of the total series*

Calendar month	Number of cases	Mean birth weight, grams	Standard deviation
I	1043	3386	519
II	681	3376	616
III	1082	3504	641
IV	1145	3452	574
V	1154	3517	527
VI	1150	3444	576
VII	1005	3417	541
VIII	1170	3462	510
IX	873	3453	588
X	923	3462	608
XI	799	3407	612
XII	906	3400	523
Total	11 931	3444	569

Table 11 *Monthly variations in births of low birth weight infants separated into preterm and term plus postterm infants and those whose length of gestation is unknown*

Calendar months	I+II	III+IV	X+VI	VII+VIII	IX+X	XI+XII	Total
Number of preterm low birth weight infants	61	55	63	41	49	45	314
Percentage of all preterm low birth weight infants	19 4	17.5	20.1	13 1	15.6	14.3	100.0
Number of term plus postterm low birth weight infants	23	32	20	30	20	29	154
Percentage of all term plus postterm low birth weight infants	14 9	20.8	13.0	19.5	13.0	18.8	100.0
Number of low birth weight infants whose length of gestation is unknow	10	5	5	2	5	4	31
Percentage of all low birth weight fants whose length of gestation is unknown	32.3	16.1	16.1	6.5	16.1	12.9	100.0
Percentage distribution of births of the total series	14 4	18.7	19.3	18.3	15.0	14.3	100.0

Table 13 *Variations in birth weights of the total series in different temperature groups representing the mean values over a period of 30 years on the day of birth*

Mean temperature C°	Number of cases	Mean birth weight, grams	Standard deviation
−12 or below	747	3332	604
−11— −8	2118	3374	598
−7— −4	1340	3490	565
−3— ± 0	1372	3492	552
+1— +4	1310	3504	584
+5— +8	1207	3447	573
+9— +12	1417	3477	548
Above +12	2420	3434	536
Total	11,931	3444	569

winter months from November to March 3 415 grams, and for the combined spring and autumn period 3 471 grams.

b) Variations in birth weight by temperature

The birth weight means were further counted in groups formed on the basis of the mean temperature on the day of birth calculated from the values of the 30 year period. The results are shown in table 13 Parallel with the increasing temperature, the mean values for birth weights are higher up to temperatures of +1 C — +4°C. Above those values the mean birth weight values are again lower than during the colder periods.

The decrease in the mean birth weight from the temperature period producing the maximum birth weight, +1 — +4 C, was gradual both in decreasing and increasing temperatures, with the exception of the temperature period of +9 — +12 C where the mean birth weight was higher than in the period before it. The significance of the differences in the means for birth weights in the lowest temperature period, 3,332 grams, and in the maximum birth weight temperature period of +1 — +4 C, 3,504 grams, was tested by the t test. The difference was highly significant, the t value being 6.34 The difference in mean birth

Table 14 *Variations in birth weights of term infants alive after the perinatal period with weight of 2500 g or more in different temperature groups representing the mean values over a period of 30 years on the day of birth*

Mean temper tur C°	Number of cases	Mean birth weight, grams	Standard deviation
−12 or below	62	3447	436
−11— −8	172	3496	446
−7— −4	115	3550	501
−3— ± 0	118	3562	464
+1— +4	111	3594	470
+5— +8	100	3527	462
+9— +12	118	3559	443
Above +12	204	3501	436
Total	1000	3529	456

weights in the temperature period of +1 — +4° C, 3,504 grams, and the mean birth weight of 3 434 grams in the highest temperature period (above +12 C) was also highly significant (t value 3.69)

To remove the influence on the figures of the preterm and low birth weight infants whose incidence in winter increased as shown above, the following calculations were made. From about 10,000 infants with a birth weight of 2,500 grams or more, whose gestational age was from 38th to 42th weeks and who were alive after the perinatal period (44) a random computer sample of every 10th was taken and their distribution over the same temperature groups as in table 13 was examined. The results are given in table 14 This finding is about the same as for the total series: with increasing temperatures the birth weights increase up to temperatures of +1 C — +4 C, but above these values the birth weights fall again. For temperatures from — 11°C to —8 C the mean value for birth weight is practically the same as for temperatures above +12 C, and only at temperatures below — 12 C does the mean birth weight remain lower than at higher temperatures.

The actual temperature values on the days of birth of the children in the present series correspond fairly well to the temperature values above zero in tables 13 and 14 On the day of birth of the infants born in the period with the temperature below zero, the temperature, in fact, was far below the figures given in tables 13 and 14 as seen on page 26 and 27

c) Seasonal variation in birth weight by sex

When the boys and girls were examined separately the monthly variation in birth weights gave the following results. Boys had highest mean birth weights in March, 3,663 grams (sd 631) and girls in May 3,545 grams (sd 504) The lowest mean for boys was in January 3 406 grams (sd 556) and for girls in February 3,263 grams (sd 557) When the seasonal variation was studied in two month periods, the highest mean for boys was in the March April period, 3,555 grams (sd 614) and for girls in the May June period, 3 447 grams (sd 526) The lowest mean birth weight for boys was in the November December period, 3 431 grams (sd 584) and for girls in the January February period, 3,335 grams (sd 517)

d) Seasonal variation in birth weight by social class

The series was divided into social classes I II + III IV and farmers and the mean birth weight was computed separately for girls and boys in two month periods. The best period for the heaviest birth weight in boys as seen above, March and April, was only valid for social class IV and farmers, as can be seen in table 15 in which the highest and lowest mean birth weights are shown by social classes. The highest mean birth weight for boys in social class I was in the September-October period and in social classes II + III in the July August period.

The best period for high birth weight means for girls, May June, was found to be valid for girls in social class I and farmers. In social classes II + III and IV the highest mean birth weights for girls occurred in the September-October period.

The lowest birth weight means for boys were in November December in social classes

Table 15 *The highest and lowest mean birth weights (grams) by social classes calculated in two month periods*

Calendar months	January February	March April	May June	July August	September October	November December
			GIRLS			
Social class I			3828		3085	
Social classes II+III				3358	3452	
Social class IV	3181				3434	
Farmers			3455			3273
			BOYS			
Social class I	3435				4007	
Social classes II+III				3637		3437
Social class IV		3650				3148
Farmers		3671				3599

II + III, IV and farmers. In social class I the lowest mean for boys occurred in January February Among the girls there was great variation by social classes in the period of the lowest mean birth weights. In farmers it was November December in class IV January February in classes II + III in July August, and in class I in September-October

The social classes showed no regular tendency to differ in any particular way from the general pattern of the seasonal variation in means of birth weights, as described above and shown in table 1_ There was a certain trend in all social classes except farmers to have the highest mean birth weight in late summer or autumn instead of spring and late winter However some groups had their lowest means in late summer and in autumn, and in none of the eight groups did the lowest mean occur in late winter or spring.

3 Seasonal variation in boy-girl ratio

Table 16 shows the monthly variations in the boy-girl ratio (number of boys per 1000 girls) of births and conceptions. There is a tendency in the series for the proportional number of male births to be highest in late winter and early spring, from February to April the boy-girl ratio being 1193 to 1361 The proportional number of male births is lowest in the July August period, the sex ratio being about 850, but figures almost as low exist in the December January period, 855 to 972.

The proportional number of conceptions of boys is highest from June to August, 1_84 to 1317 The proportional number of male conceptions is lowest in late autumn and early winter in October and December the sex ratio being 884 and 781 but the lowest figures occur in May 746 boys per 1000 girls.

4 The effect of individual climatic factors at the time of delivery

a) *The differences in mean values for climatic factors in risk groups and control groups*

The effect of different climatic factors on the prevalence of risk groups was studied by calculating the mean for each factor fo the risk group and the corresponding control group. Attention was first focused on the day of birth. Because of the great variations in value of some of the climatic factors during the year the groups were treated by the seasons of the year The significance of the difference in means was studied by a t test.

Regarding temperature, the following facts were studied. the temperature at _0.00 hours, the minimum and maximum temperatures of the day The effect of the mean temperature from over a period of 30 years was also studied, but it is clear that it is more indicative of the time of the year as a whole, because the actual temperature of the day in

Table 16. *Monthly variation in the boy-girl ratio of the total number of births and of the total number of conceptions.*

Calendar months	Birth rate: Number of boys	Birth rate: Number of girls	Birth rate: Boys per 1000 girls	Conception rate: Number of boys	Conception rate: Number of girls	Conception rate: Boys per 1000 girls
I	476	557	855	467	395	1182
II	365	306	1193	436	367	1188
III	622	457	1361	466	456	1021
IV	648	500	1296	5_6	439	1152
V	6_5	549	1102	285	382	746
VI	637	513	1242	532	407	1307
VII	463	542	854	619	470	1317
VIII	534	628	850	641	499	1284
IX	442	429	1030	617	527	1170
X	502	420	1195	438	495	884
XI	455	342	1330	514	500	1028
XII	446	459	972	379	485	781
Total	6195	5702	1086	5900	5422	1088

Table 17 *Means and standard deviations for different climatic factors on the day of birth in 61 perinatal deaths and 3,264 babies alive after the perinatal period and t-values for differences in means for these two groups of infants during the summer months June July and August*

Climatic factor	Alive after perinatal period		Perinatal deaths		t values for differences in means
	Mean	Standard deviation	Mean	Standard deviation	
Temperature at 20.00 hours °C	15 1	4.5	15.2	4.0	0.21
Minimum temperature, C	9.0	4.5	8.8	4.2	0.25
Maximum temperature, °C	18.4	4.7	18.5	4.2	0.24
Mean temperature from 30 years period, C	13.9	2.5	13.7	2.3	0.67
Relative humidity per cent	65.8	17.6	62.0	16.9	1.70
Duration of daylight, hours	19 4	2.6	19.8	2.9	1 11
Snow depth, cm	0.0	0.0	0.0	0.0	0.00

Table 18 *Means and standard deviations for different climatic factors on the day of birth in 87 perinatal deaths and 4,008 infants alive after the perinatal period and the t-value for differences in means for these two groups of infants during the spring and autumn months April May September and October*

Climatic factor	Alive after perinatal period		Perinatal deaths		t values for differences in means
	Mean	Standard deviation	Mean	Standard deviation	
Temperature at 20.00 hours, C	3.6	5 9	3 1	6.4	0.74
Minimum temperature, C	—1 4	6.7	—1.2	6.0	0.40
Maximum temperature, C	5 8	6.1	5.8	6.3	0.04
Mean temperature from 30 year period, C	3.5	4.2	3.1	4.3	0.98
Relative humidity per cent	74.6	18.1	75.3	18.3	0.39
Duration of daylight, hours	14.5	3.5	14 1	4 1	1 04
Snow depth, cm	12.7	20.0	12.1	19.5	0.3

Table 19 *Means and standard deviations for different climatic factors on the day of birth in 135 perinatal deaths and 4,376 babies alive after the perinatal period and the t-values for differences in means for these two groups of infants during the winter months November December January February and March.* (*$P<0.05$ ***$P<0.001$)

Climatic factor	Alive after perinatal period		Perinatal deaths		t values for differences in means
	Mean	Standard deviation	Mean	Standard deviation	
Temperature at 20.00 hrs, C	—12.7	9.6	—14.8	8.9	2.55
Minimum temperature, C	—17 1	11.2	—19.0	10.2	1.92
Maximum temperature C	— 8.9	8.2	—10.8	7.8	2.53
Mean temperature from 30 year period, C	— 8.9	3.3	— 9.3	2.9	3.53***
Relative humidity per cent	83.8	10.8	82.1	8.4	1.73
Duration of daylight, hours	7.2	3.2	7 4	3.0	0.71
Snow depth, cm	35.0	22.2	38.8	17 1	1.94

question could, of course, differ a great deal from the 30 years mean.

The relative humidity duration of day light and snow depth were also studied.

Perinatal mortality Table 17 shows the different climatic factors on the day of birth for 61 infants who died in the perinatal period and for 3,264 infants who were alive after the perinatal period in summer

As can be seen, there were no significant differences in the means for the perinatal deaths and living infants. Table 18 shows the same climatic variables for the 87 perinatal deaths and the 4 008 infants alive after the perinatal period in spring and autumn. In this period of the year there

Table 20. *Means and standard deviations for different climatic factors on day of birth in 263 preterm babies and 2,717 term infants and the t-value for differences in means for these two groups of infants during the summer months June July and August*

Climatic factor	Preterm infants Mean	Preterm infants Standard deviation	Term infants Mean	Term infants Standard deviation	t-value for differences in means
Temperature at 20.00 hrs, C	15.4	4.6	15.1	4.6	1.06
Minimum temperature, C	9.0	4.4	9.1	4.5	0.27
Maximum temperature, C	18.8	4.6	18.6	4.5	0.68
Mean temperature from 30 year period, C	13.8	2.8	13.9	2.5	0.65
Relative humidity per cent	64.9	18.4	65.0	17.6	0.92
Duration of daylight, hours	19.6	2.7	19.5	2.6	0.68
Snow depth, cm	0.0	0.0	0.0	0.0	0.0

Table 21 *Means and standard deviations for different climatic factors on day of birth in 340 preterm infants and 3 437 term infants and t-value for differences in means for these two groups of babies during the spring and autumn months April May September and October* (*$p<0.05$)

Climatic factor	Preterm infants Mean	Preterm infants Standard deviation	Term infants Mean	Term infants Standard deviation	t-value for differences in means
Temperature at 20.00 hrs, C	3.9	6.1	3.6	5.9	0.80
Minimum temperature, C	−1.2	6.6	−1.5	6.6	0.81
Maximum temperature, C	6.4	5.9	5.7	6.1	1.86
Mean temperature from 30 year period, C	3.9	4.2	3.5	4.2	1.98*
Relative humidity per cent	73.1	18.2	74.3	18.2	0.77
Duration of daylight, hours	14.5	3.5	14.5	3.6	0.43
Snow depth, cm	10.9	18.1	12.9	19.9	1.81

Table 22 *Means and standard deviation for different climatic factors on day of birth in 432 preterm infants and 3,711 term infants and the t-value for differences in means for these two groups of infants during the winter months November December January February and March* (**$P<0.01$ ***$P<0.001$)

Climatic factor	Preterm infants Mean	Preterm infants Standard deviation	Term infants Mean	Term infants Standard deviation	t-value for differences in means
Temperature at 20.00 hrs, C	−15.6	9.9	−12.5	9.4	6.33***
Minimum temperature, C	−20.1	11.1	−17.0	11.2	5.47***
Maximum temperature, C	−11.5	8.8	− 8.8	8.1	6.34***
Mean temperature from 30 year period, C	− 9.4	3.2	− 8.3	3.3	6.37***
Relative humidity per cent	82.1	10.7	83.8	11.0	2.90**
Duration of daylight, hours	7.61	2.7	7.1	3.3	2.83
Snow depth, cm	40.2	18.3	34.8	22.4	4.79***

was no significance in differences of means, either Table 19 shows the mean values for climatic factors in 135 perinatal deaths and 4,376 living infants in winter All the variables measuring temperature are lower in the group of perinatal deaths, but the differences in means for the temperature at 20.00 hours and for the maximum temperature of the day are no more than nearly significant. On the other hand, there is a highly significant difference between the perinatal deaths group and the living group regarding the temperature means from over a period of 30 years. As stated earlier this variable indicates, in the first place, the season, the "depth" of winter

Preterm infants. The mean values for climatic factors for preterm births com-

pared with the corresponding figures for term births are shown in tables 20, 21 and 22. The 636 postterm births are excluded from the figures. Table 20 gives the climatic figures in summer for 263 preterm infants and 2,717 term infants. In all the means the differences are without significance. Table 21 shows the difference in the means climatic factors in the spring and autumn period for 340 preterm and 3 437 term infants. For this period the difference in the 30 years mean temperature between the groups is nearly significant.

Table 22 gives the differences in means for different climatic factors for 432 preterm and 3,711 term infants in winter As can be seen, all the variables measuring the temperature show highly significant differ ences in the means for these to groups. The mean temperature at 20.00 hours for preterm infants is —15.6 C and — 12.5°C for term infants. The values for the minimum temperature are —20 1 C and — 17 0 C and for the mean maximum temperature — 11.5°C and —8.8°C respectively Also the difference in means for the 30 year period temperatures is highly significant for the groups, — 9 4 C for preterm infants and —8,3°C for term infants. The snow depth in the preterm infants group is 40.2 cm and 34.8 cm in the term baby group, the differ ence being highly significant. The relative humidity in the preterm group is significantly lower and the duration of daylight longer than in the term group in winter

Low birth weight infants. The mean values for different climatic factors in low birth weight infants and normal birth weight infants by different seasons are given in tables 23 24 and 25 Table 23 gives the results for 117 low birth weight infants and 3,208 normal birth weight infants in summer and table 24 for the same groups (155 and 3,940 infants respectively) in spring and autumn. In neither of them is there any significant difference in means between the

Table 23 *Means and standard deviations for different climatic factors on day of birth in 117 low birth weight infants and 3,208 infants with normal birth weight and the t value for differences in means for these two groups of babies during the summer months June July and August*

Climatic factor	Low birth weight infants		Normal birth weight infants		t value for differences means
	Mean	Standard deviation	Mean	Standard deviation	
Temperature at 20.00 hrs, C	15.7	4.2	15.0	4.6	1.57
Minimum temperature, C	9.0	4.6	9.0	4.5	0.07
Maximum temperature, C	18.7	4.4	18 4	4.7	0.71
Mean temperature from 30 year period, C	14.1	2.4	13.9	2.5	0.78
Relative humidity per cent	64.8	18.4	65.8	17.6	0.57
Duration of daylight, hours	19.7	2.6	19 4	2.6	1.23
Snow depth, cm	0.0	0.0	0.0	0.0	0.0

Table 24 *Means and standard deviations for different climatic factors on day of birth in 155 low birth weight infants and 3,940 infants with normal birth weight and the t-value for differences in means for these two groups of babies during the spring and autumn months April May September and October*

Climatic factor	Low birth weight infants		Normal birth weight infants		t value for differences means
	Mean	Standard deviation	Mean	Standard deviation	
Temperature at 20.00 hrs, C	2.9	5.8	3.6	5.9	1.34
Minimum temperature, C	—1 4	6.3	—1.4	6.7	0.13
Maximum temperature, C	5.4	5.8	5.8	6.1	0.83
Mean temperature from 30 year period, C	3.1	4.0	3.5	4.2	1.16
Relative humidity per cent	74.9	18.1	74.6	18.1	0.19
Duration of daylight, hours	14.1	3.9	14.5	3.6	1.18
Snow depth, cm	11.7	17.7	12.7	19.9	0.65

Table 25 *Means and standard deviations for different climatic factors on day of birth in 227 low birth weight infants and 4,284 infants with normal birth weight and the t value for differences in means for these two groups of babies during the winter months November December January February and March* (*P<0.05 ***P<0.001).

Climatic factor	Low birth weight infants Mean	Standard deviation	Normal birth weight infants Mean	Standard deviation	t-value for differences in means
Temperature at 20.00 hrs, C	—16.0	10.2	—12.6	9.5	3.30*
Minimum temperature, C	—20.1	11.2	—17.0	11.2	4.11
Maximum temperature, C	—11.7	8.6	— 8.9	8.2	4.96**
Mean temperature from 30 year period, C	— 9.7	2.9	— 8.3	3.3	6.10***
Relative humidity per cent	82.0	8.8	83.8	10.8	2.47*
Duration of daylight, hours	7.5	2.9	7.2	3.2	1 46
Snow depth, cm	40.3	17 9	34.8	22.2	3.38***

groups. Table 25 gives the means for climatic factors in winter for 227 low birth weight infants and 4,284 normal birth weight infants. All the temperature values are lower in the group of low birth weight infants than in the controls, the values being as follows temperature at 20.00 hrs —16.0 C for the risk group and —12 6 C for the controls, minimum temperature of the day —20 1 C for the risk group and — 17.0 for the controls, and maximum temperature — 11.7 C° for the risk group and — 8 9 C° for the controls. All the differences in means for the two groups compared were highly significant. Also the mean temperature value from over the 30 year period on days of birth was highly significantly lower for low birth weight infants than for normal birth weight infants, the values being —9 7 C and —8.3 C° respectively

The mean value for snow depth in the group of low birth weight infants is 40.3 cm, and 34 8 cm in the group of normal birth weight infants. The difference is highly significant. The relative humidity is somewhat lower in the low birth weight infants than in the controls, the values being 82.0 per cent and 83.8 per cent respectively The difference is nearly significant.

b) *The influence of extreme values of temperature and depth of snow cover*

When we examine the total results of the influence of the climatic factors on the prevalence of risk groups the most signif icant results were found in temperature and snow depth. Therefore these two were examined more thoroughly For each period of the year the 10th and 90th percentile values for the minimum temperature on the day of birth were calculated and similarly the 10th and 90th percentile values for the snow depth on the day of birth. The mean climatic figures representative for the study population in different periods of the year are given on page 14 In each period of the year the study population was divided into three groups according to the minimum temperature on the day of birth 1) temper ature below the 10th percentile, 2) temper ature between the 10th and 90th percentiles, and 3) temperature above the 90th per centile. Similarly when the influence of the snow depth was studied, the population was divided into three groups according to the snow depth in each period of the year

The variation in perinatal mortality rate in summer when the delivery days are grouped according to the minimum tempera ture of the day is shown in table 26.

Mortality is lowest on 10 per cent of the warmest days, 14.3 per thousand compared with the figures of 18.4 and 21.9 per thousand for the days when the minimum temperature was between the 10th and 90th percentiles and the days when it was above the 90th percentile. The differences in the mortality rate, however were not statistically significant.

Table 27 shows the corresponding figures for perinatal mortality in the combined spring and autumn period. As is seen mortality was equally low on days with temperatures below the 10th percentile as on days with temperatures above the 90th percentile. Table 28 shows the perinatal mortality rates in winter when the delivery days are divided according to the minimum temperature. The difference between the groups with temperatures below the 10th percentile and temperatures between the 10th and 90th percentile is slight, the mortality figures being 32.3 and 31.3 per thousand. The mortality figure for the warmest days, 19.5 per thousand, was lower but the difference is not statistically significant (t value 1.32)

The rate of preterm births was similarly studied by different seasons of the year when the days were divided into groups according to the minimum temperature of the day of birth. In summer and in the spring and autumn period there was no significant difference between the mortality rates for the warmest and the coldest days. Table 29 shows the results for winter The rate of preterm births is clearly lowest for the 10 per cent of the warmest days, 6.7 per cent, than for the other two groups of the days on which the preterm birth rates are 9.2 and 15.3 per cent. The difference is statistically highly significant when the rate for the warmest days is compared with the rate for the fairly cold days (t value 4.51) The difference between the rate of preterm births on fairly cold days, 9.2 per cent, and on the coldest days, 15.3 per cent, was not statistically significant (t value 1.93)

When the rate of low birth weight infants was studied by different seasons and by different degrees of the minimum temperature, the findings were similar to those for the rate of preterm births. No significant differences were found in the summer and in the spring and autumn period when studying the different degrees of temperatures on delivery days. In winter however the coldest temperature increases the rate of low birth weight infants, as is seen in table 30 On ten per cent of the warmest days the rate is 3.4 on fairly cold days 4.8 and on the coldest days 8.7 per cent. The difference between the rate of low birth weight infants on the coldest and warmest days is highly significant (t value 3.62)

Table 26 *Perinatal mortality rate per thousand in summer the days are divided into three groups according to the minimum temperature of the day of birth*

Minimum temperature	Number of deaths	Total number of cases	Mortality per thousand
Below 10th percentile	9	410	21.9
Between 10th and 90th percentile	46	2495	18.4
Above 90th percentile	6	420	14.3
Total cases	61	3325	18.3

Table 27 *Perinatal mortality rate per thousand in the combined spring and autumn period the days are divided into three groups according to the minimum temperature of the day of birth*

Minimum temperature	Number of deaths	Total number of cases	Mortality per thousand
Below 10th percentile	8	544	14.7
Between 10th and 90th percentile	74	3228	23.5
Abov 90th percentile	5	323	15.5
Total cases	87	4095	21.2

Table 28 *The perinatal mortality rate in winter when the days of birth are divided into groups according to the minimum temperature of the day*

	Number of deaths	Number of all cases	Perinatal mortality per thous
Temperature below 10 th percentile	16	496	32.3
Temperature between 10th and 90 percentile	108	3450	31.3
Temperature above 90th percentile	11	565	19.5
All cases	135	4511	29.9

Table 29 *The rate of preterm babies in winter when the days of birth are divided into groups according to the minimum temperature of the day*

	Number of preterm infants	Number of all cases	Preterm babies per ent
Temperature below 10 th percentile	76	496	15 3
Temperature between 10 th and 90 th percentile	318	3450	9 2
Temperature above 90 th percentile	38	565	6 7
All cases	432	4511	9 6

Table 30. *The rate of low birth weight infants in winter when the days of birth are divided into groups according to the minimum temperature of the day*

	Number of low birth weight inf	Number of all ases	Low birth weight inf per ent
Temperature below 10 th percentil	43	496	8 7
Temperature between 10 th and 90 th Percentile	165	3450	4 8
Temperature above 90 th percentile	19	565	3 4
All ases	227	45 1	5 0

The influence of snow depth on the rate of different risk groups was studied in the same way as the influence of temperature. The days of birth were divided into three groups according to the snow depth 1) snow depth below the 10th percentile, 2) between the 10th and 90th percentiles and 3) above the 90th percentile. The rates for three risk groups, perinatal deaths, preterm births and low birth weight infants, were studied separately by different seasons of the year except summer when no snow exists in the study area. In the spring and autumn period no significant differences were found in the rate for any risk groups according to the snow depth.

In winter however the rates of all three risk groups were higher when the snow depth was between the 10th and 90th per centiles, but the rates were nearly as low in the period when the snow depth was above the 90th percentile as in the period when it was below the 10th percentile. The extreme value for snow depth did not increase the incidence of risk groups. As stated earl er the higher snow depth exist ed only in late winter and not at all in some districts.

5 Social economic and biological factors operating parallel with the climatic factors

The first question, of course, is to think about how the influence of the climatic factors just considered works independently of other parallel factors. To study this, the population giving birth to their children on the coldest 10 per cent of days in winter 496 mothers *(the cold group)* and the population giving birth on the warmest 10 per cent of days in winter 565 mothers *(the warm group)* were taken separately and the differences and similarities of various characteristics in these two groups were compared. The distribution of some of the factors will also be compared with the cor

responding distribution in the groups containing all the inhabitants of the provinces of Lapland and Oulu.

a) The origin of the members of cold and warm groups in different parts of the study area

When the material was treated in this way the two groups representing the warmest ten per cent and coldest ten per cent of winter days did not contain proportionally the same number of mothers for the provinces of Oulu and Lapland as the total series. Of the 496 mothers in the cold group 246 mothers had their place of residence in the province of Lapland and 250 in the province of Oulu, the proportion being one half from each province instead of one third from Lapland and two thirds from the province of Oulu as in the total series. Of the 565 mothers in the warm group 137 mothers were from the province of Lapland, about one quater instead of one third, and 428 mothers were from the province of Oulu. The proportion of the births belonging to the most northerly area (Ivalo) is about 1 6 per cent in the total series (page 13) The coldest days group had 4 births belonging to that area which is about 0 8 per cent of that group Thus there was no over representation of the most northerly area in the cold group The proportion of all births belonging to the most southerly area (Kajaani) is about 21.3 per cent (page 13) The cold group had 99 births from that area which is some 20 per cent of the total group and the warm group 90 births, which is some 16 per cent of that group Thus the most southerly area was rather under represented in the group of births falling on the warmest ten per cent of days. But, for example, the inhabitants of the city of Oulu make up 15 8 per cent of the total series with 1 889 births, but in the cold group there are only 40 which is 8 1 per cent of the total group, and in the warm group there are 148 births, which is 26.2 per cent of the total group.

b) The nature of the place of residence of members in cold and warm groups

Table 31 shows the *kind of place of residence* for those who had their delivery on the coldest 10 per cent of days and the warmest 10 per cent of days in winter As can be seen when divided into groups, some 36 — 38 per cent of the members of both groups live in towns, from 23 to 27 in villages and 37 per cent in remote villages

These two populations were also compared regarding the mean *developmental level of the community where they live* To measure

Table 31 *Place of residence of the study population giving birth to their children on the coldest 10 per cent of days and on the warmest 10 per cent of days in winter and of the total population In 28 cases of the total population the place of residence was unknown.*

	Birth on coldest 10 per cent of days		Birth on warmest 10 per cent of days		Total series	
Place of residence	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Town	178	35 9	217	38.5	4.014	33.7
Village	134	27.0	138	24.5	3.242	27.2
Remote village	184	37 1	208	37.0	4.647	39 0
Total	496	100.0	563	100.0	11.903	100.0

the developmental level of the community a scoring system was used, computing 18 different indices (44) according to which the 81 communities in the study area each get a score from 1.7 to 9.3 The members of the cold group got a mean scoring of 5 0 (sd 2.6) and the members of the warm group got a mean scoring of 5 4 (sd 3 0), the value for the total series being 5.2. The difference in the developmental level of the community between the temperature groups is statistically nearly significant, the t value being 2 10

Table 32 shows the *distance to a medical officer* for the population in different temperature groups It can be seen that the distribution into different distance groups is quite similar even if there is a slight tendency for the distance to be longer in the group with births on the coldest 10 per cent of winter days. As a whole it can be said that *concerning the nature of the place of residence there is no clear difference between the mothers who had their delivery during the coldest ten per cent of days and mothers who had their delivery during the warmest ten per cent of days in winter*

c) *Differences in the level of housing between the cold and warm groups*

The mean *number of rooms* in the family dwelling was 2.5 for the population with births on the coldest 10 per cent of days, 3 0 for the population with births on the warmest 10 per cent of days, the value for the total series being 2.7 The mean size of the household (not including the child to be born) for these three groups was 3 9 4 4 and 4.3 persons, so that the number of rooms per person in the household was 0 64 0 68 and 0 65 This shows that the density of persons in the family dwellings in different groups was very similar

Table 33 shows the facilities in the family dwellings — e.g *electricity running water* and *telephone* for the population in the cold and warm groups. The difference between temperature groups was clearest concerning running water 42 9 per cent of the dwellings of the mothers in the cold group had it compared with 65.8 per cent in the other group The difference is highly significant, the t value being 7.39 The percentage of dwellings with running water in the province of Lapland in the total series is 47.7 and in the province of Oulu 53.6, so that the difference between the groups formed on the basis of the tempera ture on the day of birth is greater than between the groups formed by provinces. The dwellings with electricity were 80.7 per cent for mothers with births in the cold group and 87.2 per cent for mothers with births in the warm group The dwellings

Table 32 *Distance to a medical officer of the study population with delivery on the coldest 10 per cent of days and on the warmest 10 per cent of days in winter and of the total population. In 283 cases of the total population it was unknown*

Distance to medical officer km	Birth on coldest 10 per cent of days		Birth on warmest 10 per cent of days		Total series	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Less than 3	193	39.9	240	43.5	5.046	43.3
3—10	97	20.0	104	18.8	2.001	17.2
10—24	76	15.7	77	13 9	1.961	16.8
over 24	118	24 4	131	23.7	2.640	22.7
Total	484	100.0	552	100.0	11.648	100.0

having a telephone were 22.5 per cent for the coldest group and 27 per cent for the warmest group Even if these differences are not great, there is also a tendency here for mothers having their births on the warmest days to have better equipped dwellings. *As a whole there is a clear evidence that the average housing conditions are worse for the mothers with births on the coldest days than for mothers with births on the warmest days in winter*

d) *Differences in the social status between the members of the cold and warm groups*

Table 34 shows the *social class* distribution of the groups according to the father's occupation. Occupations were classified according to their social evaluation. Farmers were divided into two groups, the lower group limit being 8 hectares under plough, any area above that amount being allocated to class I

As can be seen in table 34 there is a clear tendency for the groups with higher temperatures on the day of birth to belong to a higher social class. 10.7 per cent of the mothers of this group were members of the highest social class and only 1 1 per cent of the mothers in the group with the lowest temperature on the day of delivery The difference between these two percentage figures is statistically highly significant, the t value being 6.31 The opposite was true for the lowest social class which included 12.3 per cent of the group with the warmest temperature on the day of birth, but 22.3 per cent of the mothers in the group with the coldest temperature on the day of delivery This difference is also highly significant, the t value being 4.25 In the total series the percentage figure for social class I in the province of Lapland is 5.0 and in the province of Oulu 7.0 and for social class IV 21.3 in the province of Lapland and 17.2 in the province of Oulu. So here again the provincial differences are smaller than group-differences according to the temperature on the day of birth.

As can be seen in table 34 there was no difference in distribution of the farmers when classified into two different classes regarding the two temperature groups.

The number of *unmarried mothers* in the coldest temperature group was 28 which is 5 7 per cent of the group. The corresponding figures for mothers in the warmest temperature group are 14 and 2.5 The difference is statistically significant (the t value 2.64) The percentage of unmarried mothers is 3.8 per cent in the southern province and 4.7 per cent in the northern province, the provincial differences being smaller than the group differences.

There is a clear difference in the social status between the temperature groups on the average the mothers who had their delivery during the coldest ten per cent of winter days were of considerably lower social status

Table 33 *Running water electricity and telephone in the family dwellings of the population with birth on the coldest 10 per cent of days and with birth on the warmest 10 per cent of days in winter and on the total population.*

Facilities of the dwelling	Birth on coldest 10 per cent of day		Birth on warmest 10 per cent of days		Total series	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Electricity	389	80.7	492	87.2	10.012	84.8
Running water	201	42.9	370	65.8	5.991	51.6
Telephone	105	22.5	153	27 4	2.446	21 4

e) *Working conditions of the members of the cold and warm groups*

41 9 per cent (202) of the mothers in the cold group had been *gainfully employed* outside their homes during the pregnancy The corresponding figure for the warm group was 38 9 per cent (219) mothers) the per centages being about the same. As shown in table 34 23 per cent of mothers in the cold group and 21 cent in the warm group were wives of farmers. 19.7 per cent of all mothers in the cold group and 22.1 per cent in the warm group *took part in dairy farming* the figures for both groups being identical or proportionally somewhat higher for the warm group

In the questionnaire the mothers were also asked if they *work mainly indoors or outdoors.* 71.3 per cent of the cold group worked mainly indoors, the corresponding figure for the warm group being 64 4 Very few mothers worked mainly outdoors, one mother in the cold group and 13 in the warm group, and about one third worked indoors and outdoors equally *The difference between the groups was not great but there was a slight tendency for the mothers with their delivery on the warmest ten per cent of days to work outdoors more than the others.*

f) *State of health and health care in the cold and warm groups*

Pregnancy complications and specific diseases are outside the scope of this part of the study The mothers were asked, how ever if they had been so *ill during the pregnancy* that they had been in bed for at least three consecutive days. The answer was positive in 48 mothers in the cold group, which is 10.7 per cent of all who answered, and in 54 mothers in the warm group which represents 10.1 per cent of mothers answering in this group the figures being very similar

The total *number of visits to the antenatal and postnatal clinics* (including the calls of a health visitor at home) were also registered. The mean number of visits, when counted in such a way that visits exceeding 8 were also considered as 8 was 6.9 in the cold group and 7.3 in the warm group The corresponding figures were 7 1 for the province of Lapland and 7 4 for the province of Oulu. 63.2 per cent of the mothers in the cold group had 8 or more visits and the corresponding figure in the warm group was 75.0 per cent, the provincial figures being 66.9 per cent for the Northern area and 76.0 per cent for the Southern area.

The *number of home deliveries* in Finland is very small. For the study population in

Table 34 *Distribution in social classes according to the father's occupation of the population with birth on the coldest 10 per cent of days and on the warmest 10 per ent of days in winter and of the total population. In 584 cases the father's occupation was unknown*

Social class	Birth on coldest 10 per cent of days		Birth on warmest 10 per cent of days		Total series	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
I	5	1 1	60	10.7	722	6.3
II	129	27.6	84	15.0	1 961	17.2
III	119	25.5	232	41.3	4,036	35.6
IV	104	22.4	69	12.3	2,064	18.2
Farmers I	34	7.3	37	6 6	905	7 9
Farmers II	76	16.1	79	14 1	1.659	14.8
Total	467	100.0	561	100.0	11.347	100.0

the province of Oulu the number of home deliveries was 90 which is 1 1 per cent of the total, and 14 deliveries occurred on the way to hospital (0.2 per cent). In the province of Lapland the total number of home deliveries was 25 which is 0.6 per cent of total, and 23 deliveries occurred on the way to hospital (0.6 per cent) Among the mothers of the cold group there were 10 home deliveries and one birth occurred on the way to hospital, the figures together representing 2.2 per cent of the group Among the mothers in the warm group there was one home delivery which is 0.2 per cent of that group *There was no measurable difference in the state of health of the mothers between the warm and cold groups but the health care was somewhat less intensive among the mothers who had their delivery on ten per cent of the coldest days than among the others*

g) *Biological characteristics of mothers in the cold and warm groups*

The mean *height* of the mothers having their delivery on the coldest 10 per cent of days in winter is 158 9 cm, sd 5 4 the mean height of the mothers having their delivery on the warmest 10 per cent of days is 160.9 cm, sd 5.8 (the mean for the total series is 160.1 sd 5.5) The difference is statistically highly significant, the t value being 5.60 The mean height of the mothers from the province of Lapland is 159 8 cm and of mothers from the province of Oulu 160.3 cm, the difference being 0.5 cm whereas the difference between the temperature groups is 2.0 cm.

The height of mothers is known to be higher in upper social classes than in lower classes. For the study population the mean height in class I is 162 1 cm and for the class IV 159.5 cm. Therefore the mean height for the cold and warm group was computed by giving to each member of each social class the mean height for this class. If the mothers in the cold group had been the typical representatives of their social classes according to the height, the group mean would have been 160.0 cm. Similarly the group mean of height in the warm group would have been 160.2 cm. The difference is of 0.2 cm instead of 2.0 cm between the true mean heights of the temperature groups.

The figures for the mean *weight* (nude weight before pregnancy) are 58 4 kg, sd 8 9 in the cold group and 61.3 kg, sd 9.5 in the warm group (59.3 kg, sd 8.6 for the total group) The difference is statistically highly significant, the t value being 4 91 The mean weight of mothers from the province of Lapland is 58.5 kg and of mothers from the province of Oulu 59 8 kg

If the members of the cold and the warm groups had been the typical representatives of their home provinces according to the weight, the group means for the cold and warm groups would have been 59.2 and 59.5 kilos, the difference being 0.3 kilos instead of 2.9 kilos between the true members of the temperature groups.

There are also social class differences in the weight of the mothers in the total series. For social class I the mean weight is 60.2 kilos and for social class IV 58 1 kilos. The wives of farmers were, however the heaviest, the mean for both farmer groups being 62.4 kilos. The group mean was also calculated for the cold and warm groups by giving to the members of different social classes the mean weight of that class. The mean for the cold group was then 59 4 kilos and for the warm group 59.3 kilos. There was no difference between the groups, the uniformity obviously being the result of the reverse portions of the II and III social classes (table 34 on page 39)

Table 35 shows the *age* distribution of the mothers in these two groups. The mothers belonging to the warm group are older 45.5 per cent of them being over 30 years of

age whereas the corresponding figure for mothers with delivery on the coldest ten per cent of days is 36.4 per cent. The difference is statistically significant, the t value for the difference in percentages being 2.98 A greater percentage of mothers in the cold group falls within the age range of 20 to 29 years, 37 4 per cent, compared with the figure of 49 per cent in the warm group There is no age difference of this kind between the provinces, the percentage figure for mothers over 30 years of age in the province of Lapland being 34 6 and 35 9 in the province of Oulu.

Table 36 shows the *parity* figures. The mothers with delivery on the warmest ten per cent of winter days are more often primiparas and parity IV or more than the mothers with delivery on the coldest ten per cent of days, so that the number of II plus III paras for the former group is 24.8 per cent and for the latter 44 4 per cent. The difference is statistically highly significant, the t value for the difference in percentages being 6.70 There is no such difference between the Northern and Southern provinces, the percentage of parity II plus III is 40 9 per cent for the former and 37.2 per cent for the latter

The difference in the number of mothers in parity group IV and over 26.6 per cent in the cold group and 38.5 in the warm group is also statistically highly significant, the t value being 4 10. The difference between the provinces of Lapland and Oulu shows a similar tendency the percentage fig

Table 35 *The age distribution of mothers when grouped according to a) the coldest and b) the warmest 10 per cent of days of delivery in winter and in the total series.*

Age Years	Birth on coldest 10 per cent of days		Birth on warmest 10 per cent of day		Total series	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Less than 20	30	6.2	28	5.0	845	7.1
20—29	279	57 4	280	49.5	6.792	57 1
30 years and more	177	36.4	257	45.5	4.257	35.8
Total	486	100.0	565	100 0	11.894	100.0

Table 36 *The parity distribution of mothers when grouped according to a) the coldest and b) the warmest 10 per cent of days of delivery in winter and in the total series*

Parity	Birth on coldest 10 per cent of days		Birth on warmest 10 per cent of days		Total series	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
I	144	29.0	207	36.7	3.888	32.7
II and III	220	44 4	140	24.8	4.571	38.5
IV and more	132	26.6	217	38.5	3.445	28.8
Total	496	100.0	564	100.0	11 904	100.0

ures for Para IV and over being 26.5 for the former and 30 1 for the latter

The rate of low birth weight infants among the precious children of the mothers was studied separately in both temperature groups. The rate of low birth weight infants among the previous children is 5.5 per cent for mothers with delivery on the coldest ten per cent of days and 6.6 per cent in mothers with delivery on the warmest ten per cent of days. The difference between the two temperature groups is not statistically significant.

Summarizing the results concerning the biological characteristics it is evident that mothers having their delivery on the coldest ten per cent of days are significantly shorter lighter younger and less often parity I and parity IV or more than mothers having the delivery on the warmest ten per cent of days The rate of precious low birth weight infants in both these groups was similar

h) *The pregnancy outcome in the warm and cold group*

The *rate of perinatal mortality* for the present children is 32.3 per thousand for mothers with births on the coldest ten per cent of days and 19.5 perthousand on the warmest ben per cent of days (table 28 on page 35). Of the 16 perinatal deaths in the cold group 10 were stillbirths and 6 were neonatal deaths. Of the 11 perinatal deaths in the warm group 5 were stillbirths and 6 were neonatal deaths. All the neonatal deaths occurred either in maternity hospitals or in the special nurseries of children's hospitals. Of the 103 perinatal deaths in the province of Lapland (mortality rate 25.5 per thousand) 53 were stillbirths and 50 neonatal deaths and of the 180 perinatal deaths in the province of Oulu (mortality rate _2.8 per thousand) 107 were stillbirths and 73 neonatal deaths. The over representation of stillbirths in the cold group was not found in the Northern pro in e

The *rate of low birth weight infants* is 8 7 per cent for the cold group and 3 4 per cent for the warm group (table 30 on page 35), the provincial figures being 4 4 per cent for the North and 4 1 per cent for the South. The *mean birth weight* for the group with delivery on the coldest ten per cent of days is 3,341 grams and 3 422 for the group with delivery on the warmest ten per cent of days. The mean value for the birth weight of all children born in winter is 3 415 grams and 3 444 grams for the total series. The figures for the provinces of Lapland and Oulu are 3 414 g and 3 460 g. The *mean birth length* of the infants in the cold group is 49.8 cm (sd 3.0) and in the warm group 50.1 cm (sd 2.1) The corresponding figures for the provinces of Lapland and Oulu are 50.1 cm (sd 2.5) and 50.3 (sd 2.5)

As is shown in table 29 *the rate of preterm infants* in the cold group is 15.3 per cent and in the warm group 6.7 per cent. The corresponding figures for the provinces of Lapland and Oulu are 9.3 per cent and 8.8 per cent. The percentage figure of *postterm births* in the cold group was 4.2 per cent and 5.5 per cent in the warm group the provincial figures being 6 1 per cent for the North and 5.2 per cent for the South. *The mean length of gestation* in the cold group is 274.3 days, sd 23.2, and in the warm group 279 1 days, sd 27 4

Of the children born on ten per cent of the coldest days 244 are *boys* 49.2 per cent, and 25_ *girls* 50.8 per cent, and of the children born on ten per cent of the warmest days 332 are boys, 58 8 per cent, and 233 girls, 41.2 per cent. The corresponding percentages are 50.3 per cent for boys and 49.7 per cent for girls in the province of Lapland and 53 0 per cent for boys and 47 0 per cent for girls in the province of Oulu.

When the outcome of pregnancies of the mothers who had their delivery on the coldest ten per cent of days is compared with the outcome of pregnancies of the

mothers who had their delivery on the warmest ten per cent of days a slight but clear difference is found the infants born to the mothers of the cold group being lighter shorter and less often boys and their gestation shorter than infants born to the mothers of the warm group

i) *Discriminant function analyses*

To see the proportional importance of the climatic factors among the other numerous factors having an influence on the rate of preterm births and low birth weight infants, two discriminant function analyses were carried out. In one of them the two groups to be separated were formed by mothers of preterm infants born in winter and by mothers of term infants whose birth weights were 2,500 grams or more and the infants alive after the perinatal period and born in winter The number of mothers of preterm infants was 432. The number of mothers of term infants was 3,750 from whom a pseudo-random computor sample representing one tenth was taken, the number in the group being 375 mothers.

25 variables shown in table 37 were used to separate the two groups. All the variables gave biological, social or economic information about the mother or her place of residence. The variables were chosen as being those which were known or were thought to have an influence on preterm deliveries. None of the variables used concerned directly the child born.

The significance of the discriminant function of the analyses was tested by Wilks lambda test with the following resul

Wilks' lambda	Degree of freedom		Significance	
	F	Fr	F	P
0 8818	25	795	4.26	<0.0005

The discriminant of the two groups was highly significant. The group means in reduced space for the analyses were —1 1607 and —1.3713 and the corresponding covariances 0.0892 and 0.0742.

Six climatic factors were used as variables in the analysis mean temperature from over a period of 30 years, temperature at 20.00 hrs, minimum temperature of the day relative humidity depth of snow cover and air pressure. All these factors were figures for the day of birth. As can be seen in table 37 the temperature on the day of birth over a 30 year period, which in the first place gives information about the point of the winter received the highest weighting of these six variables. Of all the variables it was the twelfth in descending order of discriminant power The two variables measuring the actual temperature on the day of birth were given the ordinal numbers 16th and 18th in the eigenvector (table 37) As

Table 37 *Eigenvectors for discriminant function analyses for the groups of 432 mothers with preterm delivery in winter and of 375 mothers with term delivery in winter The variables are in descending order of discriminant power only three decimals being indicated*

	Variable	Weighting on the eigenvector
1	Previous low birth weight infants	.390
2.	Hospital beds in local hospital/central hospital	.276
3.	Mother marital status	.245
4.	Character of place of residence urban or rural	.159
5	Distance to population centre	112
6.	Number of children under 15 years of age	.081
7	Distance to medical officer	.079
8	Ownership of family car	.073
9	Internal migration	.067
10.	Degree of industrialization of the place of residence	.057
11	P rity	.042
12.	Mean temperature over period of 30 years of the birthday of the child	.033
13.	Occupation of the father	.032
14.	Hemoglobin of the mother during pregnancy	.031
15	Mother posture at work	.026
16.	Temperatur at 20.00 hrs on the day of birth of the child	.010
17	Maternal weight	.006
18.	The minimum temperature on day of birth of he child	.005
19	Maternal height	.004
20.	Relativ humidity on the da of birth of the child	.003
21	Snow depth on day of birth of the child	.002
22.	Air pressure on day of birth of the child	.002
23.	Maternal age	.001
24	Maternal heart volume	.001
25	Distance to central hospital	.000

a whole, the climatic factors had medium importance among the other variables used to discriminate as a group the mothers with preterm delivery in winter from the group of the mothers with term delivery in winter

The other discriminant function analysis was carried out to separate the total group of mothers with low birth weight infants, 499 cases, and the group of mothers with normal birth weight infants, lenght of gestation from 38 to 42 weeks and the child alive after the perinatal period. The latter group was a pseudo-random computor sample, one tenth of about 10,000 mothers, thus totalling 1,000 cases.

Table 38. *Eigenvectors for discriminant function analyses for the groups of 499 low birth weight infants and 1000 normal birth weight infants The variables are in descending order of discriminant power only three decimals being indicated*

	Variable	Weighting on the eigen ector
1	Previous low birth weight infants	.895
2.	Mother s marital status	.349
	Previous abortions	.257
	Ownership of a family car	.057
5.	Number of children under 15 y ars of age	.043
6.	Hospital beds in local hospital/central hospital	.038
7	Mother s posture at work	.034
8.	Previous perinatal mortality	.033
9	Distance to medical officer	.028
10.	Distance to population centre	.023
11	Mother smoking	.017
12.	Occupation of the father	.013
13	Hemoglobin of the mother during pregnancy	.010
14.	Parity	.009
15.	Maternal age	.009
16.	Maternal weight	.008
17	Number of mothers deceased siblings	.007
18.	Internal migration	.007
19	Maternal height	.005
20.	Degree of industrialization of the place of residence	.005
1	Temperature at 20 00 hrs on day of birth of the child	.004
22.	Character of place f residence urban or rural	.002
23.	Maternal heart volume	.000
24	Distance to central hospital	.000
25.	Depth of snow cover on the day of birth	.000

The significance for this discriminant function analysis by Wilks lambda test was

Wilks lambda	Degree of freedom		Significance	
	F	F_2	F	P
0.8348	25	1473	11.64	<0.0005

The group means in reduced space were 0.5397 and 0.7322 and the corresponding covariances 0.0639 and 0.0307

The variables used in this analysis are shown in table 38 in descending order of discriminant power The variables were chosen as in the other analysis, as being those with known or presumed influence on the rate of low birth weight infants. Only two of the variables, the mean temperature from over a 30 year period and the depth of snow cover concerned climate. As can be seen they had only minor importance in the total discriminating function.

6 The influence of the climatic factors on conception

The effect on the outcome of pregnancy of climatic factors operating at the time of conception and spermatogenesis was studied by comparing the mean value for each climatic factor in the three risk groups with the means for the corresponding control group The risk groups and the corresponding control group were the same as in the other parts of the study 1) perinatal deaths — alive after perinatal period, 2) preterm births — term births, 3) low birth weight infants — normal birth weight infants. According to the calculated time of conception the risk groups and corresponding control groups were divided into three groups according to the season of the year in order to compare the climatic factors. The number of the members of risk groups by seasons were

	Summer (3 months)	Spring and autumn (4 months)	Winter (5 months)	Total
Perinatal deaths	71	102	92	265
Preterm infants	276	366	393	1035
Low birth weight infants	128	163	177	468

In 18 cases of perinatal deaths and 31 cases of low birth weight infants the first day of the last menstrual was unknown and it was not possible to calculate the time of conception.

The climatic factors studied were the same as in the earlier parts of the study temperature at 20.00 hrs, minimum temperature, maximum temperature, relative humidity duration of daylight, depth of snow cover and mean temperature from over a period of 30 years. The mean value for each factor was calculated from the individual value for each day included in each computation.

a) Conception

In order to time the occurrence of conception, the 13th, 14th and 15th day counted from the first day of the last menstrual period, was taken first. By separately comparing the means for the seven climatic factors in each of the three risk groups with the corresponding means in the control group over the three periods of the year there were in all 63 comparisons between the mean values. No statistically significant differences in means were found in any of them.

To study the climate around the time of conception in more detail the 14th day after the first day of the last menstrual period was taken together with ten days before and after it. The mean for each climatic factor was counted using the value for each of the 21 days. This method of calculating also covers the time of spermatogenesis and ovulation in addition to the time of conception.

The total number of comparisons was again 63 The difference in mean values between the risk group and the corresponding control group was found to be statistically significant on four occasions. On three of the four occasions the significant difference was found in the relative humidity The findings are shown in table 39 The relative humidity is lower for the risk groups and this finding occurs twice in summer the risk groups being the preterm infants and the low birth weight infants, and once in the combined spring and autumn period, the risk group being perinatal deaths.

The fourth significant difference in means was in the minimum temperature which was lower for the preterm group than for the term group in summer the t value for the difference in means being 2.96

b) *Period of organogenesis*

The period of organogenesis was counted as being the three four week periods following the 14th day after the first day of the last menstrual period and the means for each of the 84 days were computed. The series was again divided into the three

Table 39 *The significant differences in the means for relative humidity at the period round the conceptions between the risk group and the corresponding control group by different period of the year (**P<0 01).*

Season of year	Risk group	Values for risk group		Values for corresponding control group		value for differences in means
		Mean humidity per cent	Standard deviation	Mean humidity per cent	Standard deviation	
Spring and autumn	perinatal deaths	70 8	15.4	75 1	14 4	2.98**
Summer	preterm infants	68.1	9.0	69.7	8.8	2.76**
Summer	low birth weight infants	67 4	8.6	69 7	8.8	2.81**

periods of the year according to the time of conception, but because of the long duration of the time under consideration there are of course numerous overlappings in the course of the period.

Again 63 comparisons between the means of the climatic factors in the risk groups and the corresponding control groups were made. On one occasion the difference in means was statistically significant. This factor was the depth of snow cover in winter which was higher in the group of preterm infants, 38 6 cm, than in the group of term infants, 36 6 cm, the t value being 2.69 As a whole, there were very few differences in the means for the climatic factors in the first trimester between the risk groups and the corresponding control groups.

Discussion

1 Material and method

a) *Climate of the study area*

The climate of the study area is far warmer than could be expected from its latitude situation. Large areas of Asia and Northern America have permafrost far below the latitudes of the study area (24). This is a result of the influence of the northerly warm ocean current from the Atlantic which moderates the climate.

b) *Population of the study area*

Because of the climatic condition the study area is relatively more densely populated than other subarctic areas at the same latitude. The Finnish settlement in Northern Finland is old in ancient times the proportion of Lapps was greater but from the 14th century onwards the Finns have been the major population group

As shown in an earlier work concerning the study population, 7 817 mothers, 66.7 per cent of the total, had changed their dwelling place after the age of 15 (44) However only 8.5 per cent of the mothers who had moved were previously urban dwellers and 58.. per cent were from remote villages (44) When we add to this the fact that during the last few decades the study area has suffered from greater unemployment than any other part of the country it is more likely that the great majority of the population which has moved about in this way has moved from one place to another within the study area, and was to a large extent born in the study area

The age distribution of the study population, as can be seen in table 1 on page 15 differs from the distribution of the British parturient population (4) in that a greater proportion of mothers are members of either the youngest or oldest age group The percentage for the age group under 20 is 7 1 per cent in the present series and 5 8 per cent in the British series, and for the age group over 35 it is 18 9 cent in the present series and 12.9 per cent in the British series.

The parity distribution, as can be seen in table 2 on page 16, shows a greater number of multiparas than the British series (4) parity VIII and more is 5.3 per cent in the present series and 2.9 in the British series, the figures for primiparas being 3? 6 and 39.2 per cent. The differences between the parity figures for the British and Northern Finnish series are small, however if we compare them with the Hong Kong series (5) the primiparas represent only 10.2 per cent and Para III and over comprises 75.5 per cent of the total.

As can be seen from tables 3 and 4 on pages 16, which show the sector of economy of the study population, one third earn their living by agriculture, forestry or fishing. In spite of the low degree of industrialization in the study area, the educational level of the mothers, as can be seen in table 5 on page 16 is relatively high, as less than 2 per cent of them have not had any regular schooling.

c) *Method*

The data concerning the day of birth, birth weight and survival rate can b

regarded as extremely reliable, the reliability being essentially the result of the high number of hospital deliveries and the compentent antenatal clinic network which has been operating in Finland for more than 20 years (44)

As was discussed in an earlier work, the accurate determination of the time of conception always presents a problem for various reasons (44) Depending on the different degree of accuracy needed, the number of unknown cases varied when the number of expected dates was counted to an accuracy of one month compared with the counting of the number of conceptions to an accuracy of three days. To simplify the computing process, the number for the conceptions is also used to show the monthly variations in conceptions.

In the present study conception is calculated as occurring 266 days before the expected date. Therefore the conception period for pregnancies with expected dates, for example, in March, is not June but the period from the 8th of June to the 8th of July The difference between the percentage for expected dates in March, 10 4 per cent, d the percentage for conceptions in June, 4 per cent of the total (table 40), is not caused by the different number of totals but by the fact that part of the conceptions in June have their expected dates in February

The discussion concerning the use, advantages and limits of discriminant function analysis as a method for multivariable analysis is presented in an earlier work (44)

2. Seasonal variations in rate of expected dates births and conceptions

As can be seen in Figures 4 and 5 on page 18 the maximum rate of expected dates occurs in the March-April May period and the maximum rate of births in the April May June period, a secondary peak occurring in August. The main cause for the difference in the maximum periods, namely the period of expected dates beginning and ending one month earlier is the high rate of preterm births in the January February period (table 44 on page 67) which determines the number of births in March. The uneven distribution of postterm births also has a certain effect with a greater proportional number in summer

When compared with older Finnish figures collected by Lagerquist and Nieminevа (28) from 1904 to 1939 showing a maximum birth rate in July it is evident that in the present series from 1966 the maximum birth rate occurs earlier and there is a greater similarity between it and the figures for the latter period from 1934—39 than the earlier period from 1904—09 and it reflects the distribution curve of the urban population of the older series rather than the rural population.

The maximum number of conceptions in the present series occurs in the period from July to September In the older Finnish series the month with the maximum conception rate was calculated as being October and the reason for this was thought to be the better state of health and nutritional condition of the population after summer (28) By examining the distribution of birth rates in different social classes as shown in Figure 6 on page 20, we can find a slight tendency for the lower social groups to have the maximum birth rate later in spring and summer than the higher classes and the corresponding maximum of conceptions falling later The highest social class has the maximum figures in April and May and the lowest class in May and August, whereas classes II and III combined and farmers both have a peak in June and August. Farmers have the third peak in March and classes II + III combined in April. One possible explanation for this could be that in lower social classes the general

standard of health has improved during the summer months thus increasing fertility Correspondingly the change in the total figures in the present series compared with the old Finnish series could be explained in that the less seriously impaired general health of the present population may improve earlier in summer thus causing the maximum conception rate to fall earlier in July September instead of October as in the old series (28)

The monthly numbers of births are, of course, somewhat affected by the inconstant rate of preterm births. As is seen in table 41 on page 65 the number in births of social class IV in February is 7.8 per cent of the total number of births in that class but the corresponding figure for the expected dates is only 4.7 per cent (page 19) As a result the number of births in March in this class is some 19 per cent lower than with the births occurring in February and having their expected dates in March. This kind of influence is greatest in winter and spring and varies by social classes, class IV having the highest incidence of preterm births (11.6 per cent) and farmers the lowest (6.6 per cent) (45).

Family planning, no doubt, influences the favourite time of birth so that it falls in the spring months for several reasons. The summer is the most convenient time to treat the child as a small baby and the least convenient time for the mother to cope with the last months of pregnancy the reason for both these facts being the warmness of the summer In addition, most mothers working outside the home like to combine the maternity holiday and the summer holiday together and so to stay a longer time at home with the baby The social class differences in the maximum birth rate are most likely to be explained by more effective family planning in the upper classes.

The connection between the month of marriage and the monthly variations in birth rate has been discussed in many works (5 28 58 64) but in none of them are there any figures concerning the study population. In the present series, of the 3,302 married primaparas with a known date of marriage and the expected date (85 per cent of all primiparas) only 739 had conceptions during the first three months of marriage (the last menstrual cycle before marriage being induced in the figures) which is 22.4 per cent of all primiparas and only 6.2 per cent of the total study population The number of mothers with conception before marriage is rather high, 42.3 per cent of the married mothers whose dates were known. The percentage among mothers with an unknown date is probably even higher and therefore the percentage given 42.3 per cent, is probably lower than the true figure.

As can be seen in table 6 on page 21 17.0 per cent of all the marriages of the primiparas occurred in June and during the three summer months, 36.1 per cent of the total. After June the second most popular is December both very probably being popular because of the festival days — midsummer night at the end of June and Christmas. The distribution of the conceptions for mothers in whom conception occurred during the first three months of marriage, shown in Figure 7 on page 21 shows a high peak for August and September the second and third months after the June peak of marriages when compared with the total conception figures for the primiparas or the total series in Figure 5 on page 18

On the other hand the influence of December marriages seems to be only slight as the January conception peak is a minor one, part of which is a result of the influence of relatively high marriage rate in October and November The connection between the month of marriage and the month of the first birth in Northern Finland as a whole is quite weak, concerning only

every fifth first born child and has only a minor influence on the total figures.

The seasonal variations in the conceptions of the primiparas show a considerably lower rate in summer than the total series (Figures 5 and 7) The fluctuation in conceptions of primiparas whose conception occurred before marriage did not show any peak in summer but the peak in September occurred also in this group

The seasonal conception curve of the total series is a rising one from the lowest point in the beginning of the year to the highest in August and September and then falling again. A depression, however occurs in spring, in May (Fig. 5 on page 18) This depression is to be seen in each curve for both conceptions in May and birth rates in February independently of the basis the grouping is made, the only exception being the birth rate for social class IV in February As is seen on page 19 the reason for this exception was not the greater number of conceptions in social class IV in May than in other classes but the great number of preterm births in class IV in February The reason for the depression is unknown When the newspapers of May 1965 were examined no political or economic issue was found which could have had an inhibiting influence on the conception rate. As a rule May is not a special season for infectious diseases and neither was there any known epidemic in May 1965

May 1965 however was drier than usual, the rainfall in the study area being only 50 to 75 per cent of the monthly mean (21) Whether this factor is to be connected with the low conception rate or not is a very hard question to answer In studying the influence of climatic factors during the period of conception the most common finding was the lower relative humidity for the risk groups than for the controls This suggests a possible effect of low humidity on the low conception rate but there is a complete lack of any previous research work in this field.

As can be seen in figures 8 10 and 11 and in tables 43 44 and 46 all the risk groups showed an increased rate of births in the January and February period compared with the rate for the total series. The rate of births of perinatal deaths and low birth weight infants also increased in the November—December period but this was not the case with the group of preterm births. However when all cases of perinatal deaths with a known length of gestation were divided into preterm and term + postterm infants (table 9 on page 25) the rate of preterm perinatal deaths was also increased in the November—December period. The rate of preterm low birth weight infants in the November—December period was the same as the rate for the total series.

The effect of the season on the incidence of preterm births in a way confirms the uneven distribution of the postterm infants (table 45 on page 67) showing opposite figures when compared with preterm births — the highest incidence in summer and lowest in winter

As a whole, all the seasonal distribution curves for the risk groups were different from the curves for the total series in that they had high rates in winter Only the groups of preterm infants and preterm low birth weight infants had high birth rates in May—June too (Figures 10 and 12)

The findings of the present study with a high incidence of risk groups in winter are similar to those by Eastman concerning perinatal mortality in the United States from 1935 to 1937 (16) but dissimilar when compared with the more recent statistics in which the rate of births of premature infants and neonatal deaths was a little lower in the first three months of the year (62) However, the winter in the present study was colder than usual and thus the findings for more usual years are not precisely confirmed.

3 Seasonal variations in birth weight

The maximum mean birth weight was found in the spring and autumn period in the series. This finding is interesting even if the difference is not great, 56 grams between the spring + autumn period and winter (3 471 and 3 415 grams) and 30 grams between the spring and autumn period and summer The highest mean birth weight in the spring and autumn period was not caused by the different distribution of birth rates into seasons according to different social classes. As seen in table 15 on page 28 all social classes had maximum mean birth weight for both girls and boys either in the spring or autumn months except the middle social classes II + III, the maximum mean birth weight for boys in this group being in summer Neither was there any difference in choosing spring or autumn as a period for maximum birth weight according to social classes: in the highest social class the spring was the maximum period for girls and the autumn for boys whereas in the lowest class the spring was the maximum period for boys and the autumn for girls.

The seasonal variation in mean birth weight is best illustrated in table 13 on page, 27 in which the temperature from over a period of 30 years on the day of birth is used as a basis for grouping the series. As can be seen in Figure 2 on page 13 the mean temperature corresponds well with the seasons. In the study period the winter was far colder than usual but the difference was in the degree of coldness but not in the timing of it, January and February being the coldest months as usual.

The increased incidence of risk groups in winter has probably reduced the mean birth weight in winter but the tendency for birth weights to be lower in winter and summer than in the spring and autumn period is also seen in infants who are not members of any risk group (table 14 on page 27) On the other hand, the incidence of all risk groups was a little higher in the spring + autumn period than in summer as can be seen in tables 7 8 and 10 and nevertheless the mean birth weight was lower in summer

The factors determining the birth weight are not, of course, operating only on the day of birth but over a long period before. The timing of the deviation of mean birth weight for various risk groups has been studied intensively The mean birth weight of twins is lower than that of singletons after the 33rd or 34th week of gestation (17,33) and the differences in mean birth weights of various biological, social and economic groups are observable according to Gruenwald (16) after the 34th week and regarding the present study population after the 29th to 30th gestational week (44) On the other hand, the inadequate maternal diet before the sixth month of pregnancy (before the 20th week) was not associated with reduced birth weight (54) No discussion about the timing of the possible effect of climate on birth weight is available.

The weekly intrauterine weight gain varies in the present series from 110 to 210 grams on the average from the 26th to 40th week of gestation (44) The temperature on the days of birth gives an approximate idea of the mean temperatures for at least some weeks before birth. The seasons, as they are used in the study are of at least two months duration — even when spring and autumn are taken separately — and that seems to be enough to make the differences in mean birth weights appear independently of the fact that those children born in spring have the coldest period of the year just behind them and those born in autumn, the warmest. The growth of the child shows a seasonal variation, the growth being accelerated in spring and autumn (47) The time of the maximum birth weight in the series indicates that the same phenomenon exists even before birth.

every fifth first-born child and has only a minor influence on the total figures.

The seasonal variations in the conceptions of the primiparas show a considerably lower rate in summer than the total series (Figures 5 and 7) The fluctuation in conceptions of primiparas whose conception occurred before marriage did not show any peak in summer but the peak in September occurred also in this group

The seasonal conception curve of the total series is a rising one from the lowest point in the beginning of the year to the highest in August and September and then falling again. A depression, however occurs in spring, in May (Fig. 5 on page 18) This depression is to be seen in each curve for both conceptions in May and birth rates in February independently of the basis the grouping is made, the only exception being the birth rate for social class IV in February As is seen on page 19 the reason for this exception was not the greater number of conceptions in social class IV in May than in other classes but the great number of preterm births in class IV in February The reason for the depression is unknown. When the newspapers of May 1965 were examined no political or economic issue was found which could have had an inhibiting influence on the conception rate. As a rule May is not a special season for infectious diseases and neither was there any known epidemic in May 1965

May 1965 however was drier than usual, the rainfall in the study area being only 50 to 75 per cent of the monthly mean (21). Whether this factor is to be connected with the low conception rate or not is a very hard question to answer In studying the influence of climatic factors during the period of conception the most common finding was the lower relative humidity for the risk groups than for the controls. This suggests a possible effect of low humidity on the low conception rate but there is a complete lack of any previous research work in this field.

As can be seen in figures 8, 10 and 11 and in tables 43 44 and 46 all the risk groups showed an increased rate of births in the January and February period compared with the rate for the total series. The rate of births of perinatal deaths and low birth weight infants also increased in the November—December period but this was not the case with the group of preterm births. However when all cases of perinatal deaths with a known length of gestation were divided into preterm and term + postterm infants (table 9 on page 25) the rate of preterm perinatal deaths was also increased in the November—December period. The rate of preterm low birth weight infants in the November—December period was the same as the rate for the total series.

The effect of the season on the incidence of preterm births in a way confirms the uneven distribution of the postterm infants (table 45 on page 67) showing opposite figures when compared with preterm births — the highest incidence in summer and lowest in winter

As a whole, all the seasonal distribution curves for the risk groups were different from the curves for the total series in that they had high rates in winter Only the groups of preterm infants and preterm low birth weight infants had high birth rates in May—June too (Figures 10 and 12).

The findings of the present study with a high incidence of risk groups in winter are similar to those by Eastman concerning perinatal mortality in the United States from 1935 to 1937 (16) but dissimilar when compared with the more recent statistics in which the rate of births of premature infants and neonatal deaths was a little lower in the first three months of the year (62). However the winter in the present study was colder than usual and thus the findings for more usual years are not precisely confirmed.

infants (55.8 per cent) Of the 283 perinatal deaths 164 cases were low birth weight infants (58.0 per cent) (44) Of the 468 low birth weight infants of known length of gestation, 314 were also preterm infants (67 1 per cent) and 164 from the total of 499 low birth weight infants died during the perinatal period (37 9 per cent) The overlapping in the groups of low birth weignt infants and preterm infants was greatest. The fact that the deleterious effect of th climatic factors was heaviest on the preterm births rather than on the other risk groups may be influenced by the fact that the day of birth was also the time of registering the climatic conditions. Labour usually lasts less than 24 hours, but the factors determining the birth weight need more time to operate Some of the neonatal deaths occured some days after birth and 64 per cent of the stillbirths died before delivery (44) Even if the policy in maternity care in Finland is to induce labour as soon as possible after foetal death, a number of intrauterine deaths certainly occurred some days before the day of birth.

The difference in perinatal mortality between summer and winter is statistically significant and the highly significant difference in mean temperatures from over the 30 year period, mainly reflecting the time of winter between deaths and alive infants makes it possible that several factors typical of winter have a cumulative effect on influencing the higher mortality rate.

The depth of snow cover in winter was deeper for the risk groups of preterm infants and low birth weight infants than for the corresponding control groups, the difference being statistically significant. The extreme values above the 90th percentile did not, however increase the incidence of risk groups and in fact the incidence of all risk groups was lower when the snow depth was above the 90th percentile than when t was between the 10th — 90th percentiles. As stated earlier depths above the 90th per centile existed mainly in March and at two registration centres (Oulu and Rovaniemi) such depths were never reached. This latter fact, however does not reduce the mortality figures because central hospitals were situated in both towns and the inhabitants of these two towns and the surrounding areas generally had a lower mortality rate than the average (45) There remain some possible explanations for that finding, one being that the snow depth is significantly higher for risk groups only in so far as it correlates with low temperatures. This explanation is possibly also valid for the significance in humidity differences between the groups of preterm infants and term infants, the former registering a lower value. Although it would seem to be the case that low humidity is harmful in a cold climate, the opposite is true according to everyday experience.

6 Social economic and biological factors operating parallel with the climatic factors

There were two reasons for choosing the method used for examining the distribution and means of several characteristics for mothers and pregnancy outcomes in those groups giving birth to their children on the coldest and on the warmest ten per cent of winter days. The first reason was to avoid the commonly presented argument that it is not the climate which causes the deleterious effect but the ecological differences among the people who live in that climate. The second reason was to try to find the type of women who are easily affected by or resistant to cold.

In variables studied the differences between the warm group and the cold group were taken as evidence of different degrees of resistance to cold if the differences were independent of the regional differences in

these variables. The cold and warm groups contained members from both provinces, but the proportions within the temperature groups were different from the total series, 50 per cent of the members of the cold group came from the Northern province, the remaining 50 per cent from the South instead of *one third from the North* and *two thirds* from the South, and the warm group contained one quarter from the North and three quarters from the South.

Some biological and social factors which are commonly known to make mothers more than averagely likely to give birth to risk infants were not associated with the deleterious influence of the climate. The most important factor in this group was a mother's *pervious low birth weight infant* This is well known by many authors to worsen the prognosis for the present pregnancy (4 15 35) and it is also shown to be valid for the study population in an earlier work (44) It is further seen in the results of the discriminant function analysis for preterm births and low birth weight infants in tables 37 and 38 on pages 43 and 44 There was no significant difference in this respect r een the cold and warm groups.

arity group I and parity group IV and have a higher risk of perinatal mortality than parity groups II and III so that the curve for mortality against parity is U shaped (4 11 44). Parity is positively correlated with the birth weight of the expected child (13 22 23 44 57 60) but the correlation between gestational length and parity is low (13 57 59 60) Timonen *et al* (59) have also found that the secundiparas have more term deliveries than others. In the cold group of the present study there was a significant overrepresentation of *parity* II + III when compared with the warm group (table 36 on page 41) No such difference exists between the populations of the Northern and Southern provinces.

The third controversial factor among the biological characteristics of the mothers which determines the outcome of pregnancy is the *age* of the mothers. Increasing maternal age increases the risk to the expected child (4 11 44) The number of mothers aged 30 or over in the cold group was in the same order of magnitude as the figure *for the total series* and there was no significant difference between the Northern and Southern provinces. In the warm group, however the older age group was over represented so that there was a significant difference between the groups.

Of the biological factors, *maternal stature* operated in the same way in the cold climate as in other ecological situations. The mothers in cold group were significantly shorter than the mothers in the warm group and they were shorter than the mothers in the Northern province. The mothers in the cold group were also significantly lighter than the mothers in the warm group and somewhat lighter than the mothers in the Northern province in general. The mothers in the warm group were heavier than the population in general and that of the Southern province too. The uneven social class distribution of the mothers in the temperature groups did not cause differences in the size of the mothers in these two groups, neither was it affected by the regional differences in the stature of mothers.

This finding is interesting because little is known about the accumulation of the general maternal risk factors in a cold climate. From other types of study population it is known that the effect of and adaptation to the meteorological environment are influenced by the body build and the physiological pattern of the person involved (7) It has been found that heavily built men keep themselves warmer than light and small men during a period of cold stress (61). The finding by Robertson (49) that African children are to be distinguished from European children because of lower weight in

such conditions where nutritional factors do not affect the figures is also interesting and the author suggests that low weight may be advantageous in tropical climates because of its effect on the body heat balance.

If we take the heavier body weight as a primary factor for good cold toleration it could explain the over representation of the older mothers in the warm group The advancing age usually means a gain in weight. The higher parity figures in the warm group could be the result of the higher mean age of mothers in this group.

Maternal shortness and lightness as risk factors for the pregnancy outcome in usual circumstances are well documented in literature (3 4 56, 60) and for the present study population (44)

There was not much difference in the *working conditions* between the cold and warm groups but a slight tendency existed for the mothers in the warm group to work less indoors than the mothers in the cold group. Outdoor working usually gives physical training and the finding in the present study is probably explained by the results of the study on the physiological adjustment to cold toleration by physical training (1 2, 66—68)

Low *social status* was closely associated with poor cold toleration, the difference between the cold and warm groups was highly significant, when the number of mothers belonging to the highest and lowest social classes was compared. In addition the number of unmarried mothers was greater in the cold group. The significance of a poor socio-economic status for the risk groups is well realized in the literature (4 8 22, 38, 44 48, 51 65).

The *level of housing* no doubt determines the disposition to cold. The facilities of the family dwellings were significantly poorer in the houses of the cold group than warm group The coldness of the house is not, of course, directly associated with the facilities measured but running water for example, is certainly associated with the suitability of the building and in that way with its warmth

Health care is known to be associated with the social standing of the population as has been shown by Purola *et al* (41) Among the mothers with lower social standing in the cold group the average antenatal and natal health care was less effective than among the mothers with a higher social standing in the warm group. There was no difference in the state of health of the two groups when measured in the simple way used in the questionnaire, but a more detailed study concerning the pregnancy complications and diseases of the mothers is part of the study project (19)

There was no significant difference in the *nature of the place of residence* between *the warm and the cold* groups. This *finding* most certainly excludes the possibility that the significant differences in several factors between the members of the cold and warm groups were due to the ecological differences of their domiciles.

Of course there are some chance members in both groups, the time of delivery happened to be on a cold or warm day It seems to be very clear however that some of the members of the cold group are picked out as victims of the cold climate, independent of where they live. They are victims of the cold because of their poor cold toleration. Similarly the members of the warm group have better resistance to cold or have better facilities against the cold such as warmer houses and so on. Because the cold has picked out people with the lowest cold toleration the remaining population has on the average a higher toleration of cold. As a result, the members of the extreme temperature groups are, on the average, dissimilar enough to give significance to the differences which distinguish them.

7 The results of discriminant function analyses

The results of discriminant function analyses give some idea of the complexity of the environmental and individual factors which operate as causal or co-joined determinants to influence the incidence of poor pregnancy outcome.

The groups at risk to be separated from the controls were the preterm infants born in winter (table 37 on page 43) and low birth weight infants (table 38 on page 44) Of the variables used some are discussed in an earlier work (the following variables in table 37 — nos 1 3—11 13 15 18 23 and in table 38 — nos 1—5 7—12, 14—20 22) (44) and some will be considered in a later part of the study project (the following variables in table 37 — nos. 2, 14 22, 24 2 and in table 38 — nos 6 13 23 24) (45) Many factors seen to have importance in the analyses were not associated with the factors which predisposed the mothers to the deleterious effects of extreme cold The climatic factors did not have a very prominent position in the analyses, not even in the alyses concerning the preterm infants rn in winter

e weightings of the variables in the eigenvectors of the analyses by no means give the exact measurement of the importance of the variables in all possible circumstances. On the contrary the effect of individual variables in the discrimination depends on all the other variables used, and in another context the effect would be different. However in an earlier work (44) it was shown that when the cases of the study population were classified according to the chances of the different degree of risk for each case obtained in the discriminant function analysis, the results give as wide a variance in pregnancy outcomes as are seen in the natural population in the world. The variables used were all the characteristics of the mothers and none of them concerned mothers diseases nor the child born. Yet the discriminant function analysis separated a risk group of about 4 per cent of the total corresponding to that of the Indian population when measured according to perinatal mortality rate of low birth weight infants, mean birth weight and length at birth. About ten per cent obtained a risk as high as the USA negro population and one third was similar to the mean study population. About one half of the study population enjoyed a pregnancy outcome as good as in Sweden, with a mortality rate of about one quarter of that in India and a mean birth weight of over 500 grams higher The tests of significance for the discriminant power of the analyses in the present study show the results to be as good as in the earlier work (44)

8 The pregnancy outcome in the extreme temperature groups in winter

In the group of births on extremely cold days the perinatal mortality and the rate of low birth weight infants and preterm births was higher than in the group of births on warm days. The mean birth weight, length at birth and duration of gestation was also lower in the cold group Yet the importance of this finding is not in the body dimensions nor in the days of gestations but in all the ill effects they cause. The risk groups mean that a far greater number of their members, even if alive, are handicapped, need more hospital beds in the newborn period and later their incapacity will last into adult life and mean expense to the community and unhappiness to the individuals concerned. Further the level of perinatal mortality not only measures the number of deaths but also the health of the surviving children in the same group Nixon (34) has expressed it by saying like an iceberg, we see only a proportion of the ill results, the deaths

9 The effect of climate on conception and organogenesis

The results in the study regarding climatic influences on conception were rather unexpected there were no significant differences between the risk groups and the corresponding control groups in winter but there were some positive findings in summer and in the combined spring and autumn period.

In this respect the great bias of the present study project is, however that it comprises only pregnancies with a minimum weight of 600 grams at birth, the earliest week of gestation for the study population being the 25th week (44) It has been shown in many works that foetal deaths re more numerous in the earlier weeks of gestation. According to the study by French and Bierman (14) from Hawaii, of 1 000 pregnancies reaching the 4th week of gestation only 775 mothers were still pregnant at the 24th week, the other pregnancies having ended in loss of the conceptus. In the Hawaii study there were more than twice as many early (under 20 weeks) foetal deaths as late (69) The findings by Shapiro *et al* (52) concerning the New York population were similar in timing the greatest foetal loss from 1 000 pregnancies 68 were lost before the 12th week of gestation, an additional 49 pregnancies were lost before the 20th week and the number of foetal loss at the 20th week and later was only 19 The figures did not include illegal abortions and the cases in which the pregnancy was unknown to the woman herself (52)

The present study did not cover early foetal loss but only the possible foetal damage early in pregnancy in foetuses surviving up to the minimum weight of 600 grams. This certainly modifies the results obtained.

The significant differences in climatic factors between the risk and control groups were found only in summer and the combined spring and autumn period for conceptions. It seems correct to connect the very low conception rate in May — measured by pregnancies lasting until at least 24 gestational weeks — with this. There was not necessarily a small number of conceptions in May and early June, but possibly an unusually high rate of early foetal loss among the spring conceptions. Nevertheless this is not enough to explain the causative effect of lower humidity at the time of conceptions of the risk groups (table 39). The dryness in May 1965 even if it was observed in nature, was nothing to make one feel uncomfortable. The correlation between these two things does not necessarily mean a causative relationship between them. Because of the complexity of the problem and the scarcity of our knowledge about many factors connected with it, it is not possible to give any definitive answer to the questions arising from this finding

The significant differences between the risk and control groups during the time of organogenesis were very sparse: only for the preterm infants was depth of snow cover higher than for the controls in winter On the whole, the scarceness of the positive findings during the period of conception and organogenesis when compared with findings at the time of birth may be explained by the fact that most of the causative factors determining the incidence of risk groups operate in the later part of pregnancy

10 General discussion

The discussions about the physiological mechanisms which might induce labour during the cold stress are outside the scope of this study project. The cold increases the metabolic rate and is a stress for the circulatory system. The cold could also ha e

reflectoric effect via cutano-visceral systems. The search for the answers to these questions is an object of other types of study projects.

The results of the present study have clearly shown the deleterious effect of a severe winter on the pregnancy outcome. The incidence of all risk groups was higher in winter than in other seasons (tables 7 8 and 10 on pages 23—25) Further on the day of birth, the temperature was significantly lower in winter for the risk groups than for the corresponding control groups (tables 19 22 and 25 on pages 31—33) When the influence of extreme cold was studied, the incidence of risk groups was found to be increased (tables 28—30 on page 35)

As could be expected some types of mothers were more easily affected by cold than others. The mothers who gave birth to their child on extremly cold days were significantly *shorter* and *lighter than others.* This difference in size was not connected with the regional or social class differences of the groups compared (page 40) There is no reason to believe that this highly significant finding occurred by chance. The other striking characteristics of the mothers belonging to the cold group was their lower social status (page 38) The mothers of the lowest social class very probably work more outdoors than the mothers of the highest class. Therefore the finding that the mothers of the cold group work less often outdoors than the mothers in the warm group (page 39) gives the impression that working outdoors was not connected with the poorer cold toleration of the lowest social class. On the other hand, the mothers of the cold group had a poorer housing level which may very well be connected with the poor cold toleration of the lowest class. The clothing of the mothers was not studied in the project. Neither was there any measurement of how much the different social classes had outdoor exposure to cold without physical training (work).

A study like the present one, which seriously searches for all the possible ill effects the climate may have, neglects the possible favourable characteristics of the same climate. The total result of the pregnancy outcome of the study population is not poor if compared with many other countries (44).

Because of developing techniques, the struggle to make the journey from one part of the earth to another shorter and possibly because of the rapid expansion of world population, the arctic and subarctic regions are getting more concern. Thus it is not only the population which is native to this area which needs the information about the disadvantages of the subarctic climate and the resources to eliminate them.

Summary

The study covers 11 931 mothers with a single birth in North Finland. The study concerning maternal factors was prospective and comprised all the mothers with expected dates of delivery in 1966. Data comprising 96 per cent of all births in the region was obtained.

The study area is situated around the arctic circle and extends about 250 kilometers on both sides of it. The study population is native in the area. The winter of the study period was a very cold one, only twice or three times in a period of a hundred years is the winter as cold in the area.

The rates of births and conceptions were some 25 per cent higher in summer from June to August, than in the three winter months, from December to February.

There were some social class differences regarding the time of maximum birth rate, the upper class showed a maximum rate earlier in the spring and the lowest class in late spring and summer. The possible tendency of summer to improve the general health of the population and in that way to increase the number of conceptions in late summer and autumn is discussed.

The relationship between the time of marriage and the time of the first birth was a weak one. 22.4 per cent of the primiparas had conception during the first three months of marriage whereas 42.3 per cent of them had had conception before marriage.

The mean birth weight was slightly higher in spring and autumn than in the other seasons. The difference was not caused by the dissimilar distribution of birth rates among social classes. It was thought to be an expression of the general phenomenon that growth is accelerated in spring and autumn.

The conception of boys was highest in summer and lowest in late autumn and winter.

In the study three risk groups were studied separately. The groups were 1 035 *preterm infants*, 499 *low birth weight infants* and 283 cases of *perinatal deaths*. The birth rate of all three risk groups increased in winter when compared with the total series. There was a significant difference ($P<0.01$) in perinatal mortality in summer and winter the figures being 18.3 and 29.9 per thousand. The incidence of preterm births was 7.9 per cent in summer and in winter 9.6 per cent, the difference being nearly significant ($P<0.05$). The incidence of low birth weight infants was 3.5 per cent in summer and in winter 5.0 per cent, the difference being significant.

The influence of seven climatic factors on the incidence of risk groups was studied. The climatic factors were: temperature at 20.00 hours, the minimum temperature of the day, the maximum temperature of the day, relative humidity, duration of daylight, snow depth and the mean temperature from over a 30 year period for the day. The influence of climatic factors on the risk groups was studied separately in three different seasons: summer, winter and the combined spring and autumn period. The periods of pregnancy studied were: the time of conception, th time of organogenesis (first trimester) and the day of birth.

First, the significance of the differences in means for each climatic factor between th risk group and the corresponding con

group was tested. 63 comparisons were made for each period of pregnancy because the risk groups were tested separately for each of the three seasons.

Most of the significant differences were found on the day of birth. All of these significant differences occurred in winter Of the three risk groups the preterm infants had the greatest differences in climatic factors when compared with the control group and the group of perinatal deaths had the lowest differences.

The most important factor was tempera ture, a low temperature increasing risk. The influence of cold was further studied by dividing the days of births in winter into three groups according to minimum temper ature of the day: temperature below the 10th percentile (—31,3°C) temperature above the 90th percentile (—2 8°C) and tempera ture between the 10th and 90th percentiles.

The difference in the incidence of risk groups, when the coldest and warmest ten per cent of days were compared, was highest for the preterm infants, 15 3 per cent for the cold and 6.7 per cent for the warm group, the difference being highly significant ($P < 0\,001$) The difference in the incidence of low birth weight infants was also highly [illegible] the figures being 8.7 per cent for [illegible] cold group and 3 4 per cent for the warm group. The perinatal mortality rate also varied, 37.3 per thousand in the cold group and 19.5 per thousand in the warm, but the difference was not statistically significant.

The cases of delivery during the coldest ten per cent of winter days *(cold group) and during the warmest ten per cent of* winter days (*warm group*) were examined as groups. From the great number of preterm births in the cold group it was concluded that part of the members of the cold and warm groups are in those groups purely by chance, the time of delivery happened to be on that particular day but part of the mothers are members of the cold group because of their poor cold toleration and similarly the others are more likely to be members of the warm group because of their better toleration.

Several social economic and biological factors for the mothers and the pregnancy outcomes were studied in the groups. The members of the cold group did not originate in the southern part of the study area as often as in the total series and the opposite was true for the warm group. Therefore special attention was paid to exclude other ecological factors than climatic when the characteristics of the members of the cold and warm group were compared.

The mothers in the cold group were signif icantly shorter than the mothers in the warm group The members of the cold group were also lighter than the members of the warm group both differences being highly signif icant. The type of body-build was thought to be directly connected with the individual capacity to resist cold.

There was not a great difference in the working conditions between the groups, but a slight tendency was found for the mothers in the warm group to work outdoors more than the mothers in the cold group

The highest social class was under-repre- sented and the lowest class over-represented in the cold group and when compared with the figures in the warm group the difference vas highly significant. There were significantly more unmarried mothers in the cold group than in the warm group. There was also a significant difference in the housing level between the temperature groups, the mem- bers in the cold group having poorer facilities in their family dwellings. The members of the cold group also had less effective health care than the members of the warm group.

Of the common maternal risk factors, in- creasing age of the mothers and parity I and parity IV and more were more typical of the members in the warm group than the cold. On the average the children born in the

cold group had lower birth weight, shorter length at birth and shorter duration of gestation. The influence of these characteristics on the later prognosis of the child is discussed.

Two discriminant function analyses to separate the risk groups from the corresponding control groups were made using as discriminant variables some of the climatic factors and many of the maternal characteristics which are known to influence risk. According to these the climatic factors as a whole play a role of only medium or low importance in the whole complexity of environmental and individual factors connected with the question.

Only a few significant differences in the means for climatic factors between the risk groups and control groups were found around the time of conception. Of the 63 comparisons made concerning the 21 day period around conseption the differences were significant on four occasions, three of the four occurred in summer and one in the combined spring and autumn period. The number of conceptioins was counted from the births of children of minimum birth weight 600 grams — duration of gestation more than 24 weeks. The number of conceptions was very low in late spring. It was thought that possible it was not in fact a question of a decreased number of conceptions but of an increased number of early foetal losses. Of the 63 comparisions in climatic factors concerning the time of organogenesis there was only one occasion when a significant difference was obtained between risk and control groups. This occurred in winter

Acknowledgements

I wish to express my sincere thanks to all those who have contributed to the completion of my study. The help of the following people was invaluable.

Mr Kalevi Valtanen, Licentiate of Philosophy, Finnish Meteorological Institute, Helsinki, has helped me to collect the climatic data used in the study and has supervised the meteorological parts of the manuscript.

The analysis of the data was started in the first half of 1969 during my stay in Manchester. Mr Alan Gibbs, B.A., Department of Social and Preventive Medicine, University of Manchester, helped me during this part of the study work.

The greatest part of the mathematical analyses was carried out in the Institute of Electronic Data Processing of the University of Oulu and in the State Computer Centre in Oulu. Mr Kari Säkkinen, B.Sc., Mr Auno Siikaluoma, B.Sc. and Mr Timo Kuronen, B.A. did the computing work.

Professor A. M. Thomson, MRC Reproduction and Growth Unit, Princess Mary Maternity Hospital, Newcastle upon Tyne, Dr Gerald Neligan, Princess Mary Maternity Hospital, Newcastle upon Tyne and Dr John Dobbing, M.B., B.S., M.C.Path., Department of Child Health, University of Manchester showed a keen interest in this project during my visit to their Departments in autumn 1970. The discussions with them were most helpful.

Professor Leo Hirvonen, Head of the Department of Physiology of the University of Oulu, gave me some valuable advice on the physiological points of this study.

Professor Ole Wasz Höckert, Head of the Department of Pediatrics and Professor Pentti A. Järvinen, Head of the Department of Gynaecology and Obstetrics at the University of Oulu offered some final criticism.

Professor Tuomas Peltonen, Director of the Department of Pediatrics in the University of Turku gave me his continuing support and encouragement.

Mr R. Wimbury, B.A. (Reading) revised the English manuscript.

Miss Liisa Jakkula made the secretarial work and Mrs Pirkko Orell kindly helped me in gathering the literature. Mrs Seija Nieminen drew the graphs.

Part of the computing work was supported by financial aid from The National Pension Institute of Finland.

Oulu, June, 1971

P. R.

References

1. Andersen, K. L., Hammel, H. T. Hilder J. A. and Wilson, O. A field study of physiological adjustment to increased muscular activity with and without cold exposure. *Acta Univ Lund sectio II* no 11 1966.
2. Andersen, K. L., Hammel, H. T. Hilder J. A. and Wilson, O. A field study of physiological adjustment to increased muscular activity with and without could exposure. *Acta Univ Lund sectio II* no 20, 1966.
3. Billewicz, W. Z. and Thomson, A. N.: The effect of maternal social class and stature upon the incidence of prematurity. *Proc Nutr Soc 16*:5, 1957
4. Butler, N. R. and Bonham, D. G. Perinatal mortality. E. & S. Livingstone LTD Edinburgh and London, 1963
5. Chang, F. S. P. Chan, W. D. Low W. D. and Ng, C.K.: Climate and conception rates in Hong Kong. *Hum Biol 35*:366, 1963
6. Collmann, R. D. and Stoller A. A survey of mongoloid births in Victoria, Australia, 1942–1957 *Amer J Public Health 52* 813, 1962.
7. Dill, D. B., Adolph, E. F. and Wilber, C. G. Handbook of Physiology Section 4 Adaptation to the environment. Amer Physiological Soc, Washington, D.C., 1964
8. Donabedian, A., Rosenfeld, L. S. and Southern, E. M. Infant mortality and socioeconomic status in metropolitan community *Public Health Rep, 80* 1083, 1965
9. Edwards, J. H. Congenital malformations of the central nervous system in Scotland. *Brit J Prev Soc Med 12* 115 1958.
10. Eastman, P. R. Infant mortality in relation to month of birth. *Amer J Public Health 35*:913 1945
11. Feldstein, M. S. and Butler, N. R. Analysis of factors affecting perinatal mortality multivariate statistical approach. *Brit J Prev Soc Med 19* 128, 1965
12. Fine, B. J. and Gaydos H. F. Relationship between individual personality variables and body temperature response patterns in the cold. *Tech Rept EP—106 Quartermaster Research and Engineering Center Natick Mass.* March 1959
13. Fraccaro M. A contribution to the study of birth weight based on an Italian sample. *Ann Hum Genet* 20 282, 1956.
14. French, F. E. and Bierman, J. M. Probabilities of fetal mortality *Public Health Rep 77*:835, 1962.
15. Gardiner E. M. and Yerushalmy J. Familial susceptibility to stillbirths and neonatal deaths. *Amer J Hyg 30* (Sec A) 11 1939
16. Gruenwald, P. The fetus in prolonged pregnancy *Amer J Obstet Gynec 89* 503, 1964
17. Gruenwald, P. Growth of the human fetus. *Amer J Obstet Gynec 94* 1120, 1966.
18. Guthkelch, A. N. Studies in spina bifida cystica III Seasonal variation in the frequency of spina bifida births. *Brit J Prev Soc Med, 16* 159 1962
19. Hartikainen, A. L., Kokkonen, J. and Rantakallio, P. to be published.
20. Hippokrates The general works of Hippokrates. Translated by F.Adams. Sydenham Society London 1945.
21. Ilmatieteellinen Keskuslaitos. Kuukausikatsaus Suomen ilmastoon. *Valtion julkaisutoimisto.* Toukokuu no 5 vuosikerta 59 1965.
22. Jayant, K. Birth weight and some other factors in relation to infant survival. A study on an Indian sample. *Ann Hum Genet 27*:261, 1964
23. Karn, M. N. and Penrose, L. S. Birth weight and gestation time in relation to maternal age, parity and infan survival. *Ann Eugen, 16* 147 1951
24. Kimble, G. H. T. and Good. D. Geography of the Northland New York, Wiley 1955
25. Knobloch, H. and Pasamanick, B. Seasonal variation in the births of the mentally deficient. *Amer J Public Health, 48* 1201 1958
26. Knobloch, H. and Pasamanick, B. Mental subnormality *New Eng J Med,* 266:1045, 1962.
27. Knobloch, H. and Pasamanick, B. Mental subnormality *New Eng J Med,* 266 1092, 1962.
28. Lagerqvist, U. and Niemineva, K. Huomioita kuukausittaisesta syntyneisyydestä Suomessa. Observations on the monthly birthrate in Finland. *Duodecim, 65* 602, 1949
29. Marshall, E. L. A review of American research on seasonal variation in stature and body weight. *J Pediat 10*:819 1937
30. M Keown, T. and Record, R. G. Seasonal incidence of congenital malformations of the central nervous system. *Lancet, 1* 192, 1951
31. Mellin, G. W.: Fetal life tables. A means of establishing perinatal rates of risk. *JAMA, 180* 11 1962.
32. Millis, J. The effect of an equatorial climate on birth weight and subsequent weight of infants *J Trop Pediat,* 3 105, 1957
33. Naeye, R. L., Benirschke, K. Hagstrom, J. W. C. and Marcus, C. C.: Intrauterine growth of twins as estimated from liveborn birth weight data *Pediatrics, 37*:409 1966.
34. Nixon, W. C. W.: in Perinatal mortality E. & S. Livingstone LTD Edinburgh and London, 1963
35. Ounsted, M. Maternal constrain of foetal grow h in man. *Develop Med Child Neurol, 7* 479 1965
36. Pasamanick, B., Dinitz, S. and Knobloch, H. Geographic and seasonal variations in births. *Public Health Rep, 74* 285, 1959

37 Pasamanick, B., Dinitz, S. and Knobloch, H. Socio-economic and seasonal variations in birth rates. *Milbank Mem Fund Quartet, 38* 248, 1960.
38. Peltonen T and Kasanen, A. Keskosten ennusteeseen vaikuttavista tekijöistä Turun lasten klinikan vuosien 1941—53 aineiston perusteella. The factors influencing the prognosis of premature infants on the basis of material from the children s clinic in Turku 1941—1953. *Duodecim 71*·517 1955
39 Perlstein, M. A. and Hood, P H.: Seasonal ariation in congenital cerebral palsy *Develop Med Child Neurol, 9* 673, 1967
40. Petersen, W F and Mayne, A.: Cytoplasmic modification of genetic trends. *JAMA, 121*·929 1943
41 Purola, T Kalimo, E., Sievers, K. and Nyman, K. The utilization of the medical services and its relationship to morbidity health resources and social factors. *Publications of the N tional Pensions Institut Series A 3* Helsinki 1968.
42. Rai, R. M. Physiological responses to cold of newcomers and esidents of high altitude. Human Adaptability to environmentz and physical fitnes. ed. M. S. Malhotra. *Publ. Defence Institut f physiology and allied sciences. Ministry f Defence Government of India*, 1966.
43 Ramaiah, T J and Narasimham, V L.: Birth weight as measure of prematurity and its relationship with certain ma ernal factors. *Indian J Med Res 55*:513, 1967
44. Rantakallio, P Groups at risk in low birth weight infants and perinatal mortality *Acta Paediat Scand suppl. 193* 1969
45 Rantakallio, P to be published.
46. Record, R. G.: Anencephalus in Scotland. *Brit J Prev Soc M d 15* 93 1961
47 Reynolds, E. J. and Sontag, L. W: Seasonal variations in weight, height and appearance of ossification centres. *J Pediat 24*·524 1944.
48. Rider R. V Taback, M. and Knobloch, H.: Associations between premature birth and socioeconomic status. *Amer J P blic Health 45* 1022, 1953
Roberts, D F Effects of race and climate on human growth as exemplified by studies on African children. in Human Growth, p. 59 ed. by J. M. Tanner Pergamon Press, Oxford—London—New York—Paris 1960.
50. Sarkar D Birth weight in hospital sample from south India. *Indian J Pediat 35* 266, 1968
51 Shapiro, S., Weiner L. and Densen, P M. Comparison of prematurity and perinatal mortality in general population and in the population of a prepaid group practice medical care plan. *Amer J Public H alth 48* 170, 1958.
52. Shapiro, S., Jones, E. W and Densen, P M. A lif table of pregnancy terminations and correlation of fetal loss. *Milbank Mem Fund Quart, 40* 7 1962.
53. Slatis, H. M. Seasonal ariation in the American li birth sex ratio. *Ame J Hum Gen 5* 21 1953
54 Smith, C. A. Effects of maternal undernutrition upon the newborn infant in Holland (1944—1945) *J Pediat 30* 229 1947
55. Stevenson, S. A., Garver K. L. and Siegel, E. Premature full-term infants. *Amer J Dis Child 94* 169 1957
56. Thomson, A. M. and Billewicz, W Z. Nutritional status, maternal physique and reproductive ffiaciency *Proc N tr Soc 22*:55, 1963.
57 Timonen, S., Vara, P and Lokki, O: Constitution at birth and duration of pregnancy as indicators of the feotomaternal relationship. *Ann Chir Gynaec Fenn, 53* 329 1963
58. Timonen, S., Franzas, B. and Wichmann, K.: Photosensibility of the human pituitary *Ann Chir Gynaec Fenn. 53* 165, 1964.
59 Timonen, S., Vara, P Lokki, O and Hirvonen, E.: Duration of pregnancy *Ann Chir Gynaec Fenn, 54* suppl. 141 1965.
60. Timonen, S., Uotila, U., Kuusisto, P Vara, P and Lokki, O.: Effect on certain maternal, foetal and geographical factors on the weight and length of the newborn and on the duration of pregnancy *Ann Chir Gynaec Fenn, 55* 196, 1966.
61 Tromp, S. W Weather climate and man. in Handbook of Physiology, section 4.283 edited by D B. Dill, E. F Adolph and C. G. Wilber American Physiological Soc, Washington, D C., 1964
62. V tal and health statistics: Weight at birth and cause f death in the neonatal period United States, Early 1950. *National Center Health Statistics, series 21* no 6, 1965
63 V tal and health statistics. Analytical studies: Infant and perinatal mortality in Scotland. *N tional Center H alth Statistics, series 3* no 5, 1966.
64 Vital and health statistics: Seasonal ariation of births United States, 1933—63 *National Cent Health Statistics, series 21* no 9 1966.
65 Willie, C. V and Rothney W B.: Racial, ethnic and income factors in the epidemiology of neonatal mortality *Amer Sociol Rev 27*·522. 1962.
66. Wilson, O Munkner T Sorensen, S. S., Fogh, J. and Rerup, C. A field study of physiological adjustment to increased muscular acti ity with and without cold exposure. *Acta Univ Lund sectio II* no 17 1966.
67 Wilson, O and Hedner P A field study of physiological adjustment to increased muscular activity with and without cold exposure. *Acta Univ Lund sectio II* no 18, 1966.
68. Wilson, O: Field studies on the effect of cold on man w th special referents to metabolic rate. *Acta Univ Lund, sectio II* no 21 1966.
69 Yerushalmy J Bierman, J M., Kemp, D H., Connor A. and French, F E.: Longitudinal studies of pregnancy on the island of Kauai, Territory of Hawaii. *Amer J Obstet Gynec 71*: 80, 1966.
70 Zelnik, M. Socioeconomic and seasonal ariations births. A eplication. *Milbank Mem Fund rt 47*:159 1969

Table 40. *Monthly variations in births expected dates of births and estimated conceptions in the total series The monthly variation of each is also calculated as an index with the average monthly number of births (expected dates conceptions) for a year equalling 100*

Calendar months	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Total
Number of births	1043	681	1082	1145	1154	1150	1025	1170	873	923	799	906	11 931
Percentage of all births	8.7	5.7	9 1	9.6	9.7	9.6	8.4	9.8	7.3	7.7	6.7	7.6	100.0
Index showing the deviation from the annual average of 100 births per month	103	75	107	117	114	118	99	116	89	91	82	89	100
Number of expected dates	956	609	1225	1146	1197	1060	1029	1043	931	842	876	893	11,807
Percentage of all expected dates	8.1	5.2	10.4	9.7	10.1	9.0	8.7	8.8	7 9	7 1	7 4	7.6	100.0
Index showing the deviation from the annual average of 100 expected dates per month	96	68	122	118	120	110	103	104	96	84	90	89	100
Estimated number of conceptions	863	803	922	945	677	950	1089	1140	1144	933	1024	864	11,354
Percentage of all conceptions	7.6	7 1	8.1	8.3	6.0	8.4	9.6	10.0	10.1	8.2	9.0	7.6	100.0
Index showing the deviation from the annual average of 100 conceptions per month	91	85	97	100	72	100	115	121	121	99	108	91	100

Table 41 *Monthly variations in births in different social classes according to the father's social class In 584 cases it remains unknown.*

Calendar months	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Total
Number of births in social class I	60	29	59	89	110	57	61	32	49	47	78	51	722
Percentage of births in social class I	8.3	4.0	8.2	12 3	15.2	7 9	8.5	4 4	6.8	6.5	10.8	7 1	100 0
Number of births in social classes II and III	534	320	464	619	480	597	524	607	401	527	425	499	5997
Percentage of births in social classes II and III	8.9	5.3	7.7	10.3	8.0	10.0	8.7	10.1	6.7	8.8	7 1	8.3	100 0
Number of births in social class IV	137	160	183	203	248	191	173	234	179	126	93	137	2064
Percentage of births in social class IV	6.6	7 8	8 9	9 9	12.0	9.3	8.4	11.3	8.7	6.1	4.5	6.6	100 0
Number of births among farmers	224	132	322	193	223	260	175	259	205	193	164	214	2564
Percentage of births among farmers	8 7	5.2	12.6	7.5	8.7	10.1	6.8	10.1	8.0	7.5	6.4	8 4	100 0
Total	935	641	1028	1104	1061	1105	933	1132	834	893	760	901	11 347
Percentage of total	8.4	5.6	9.1	9.7	9 4	9.7	8 2	10.0	7 4	7.9	6.7	7 9	1[illegible]0

Table 42. *Monthly variations in conceptions for the primiparas. The primiparas in who the interval between marriage and expected date was more than one menstrual peri shorter than normal length of gestation and the primiparas with the conception during t three first months of marriage and those with conception after three first months of ma riage are given separately*

Calendar months	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	To
Number of conceptions of all primiparas	278	252	245	316	187	243	290	312	370	283	301	225	3,3
Percentage of all conceptions of primiparas	8.4	7.6	7.4	9.6	5.7	7.4	8.8	9.4	11.2	8.6	9.1	6.8	100
Number of conceptions of primiparas in whom conception occurred before marriage	120	161	116	130	87	118	118	112	171	120	62	80	1,3
Percentage of all primiparas in whom conception occurred before marriage	8.6	11.5	8.3	9.3	6.2	8.5	8.5	8.0	12.3	8.6	4.5	5.7	100
Number of conceptions of primiparas in whom conception occurred during the three first months of marriage	68	16	43	61	26	36	75	102	118	77	79	38	739
Percentage of all primiparas with conception in the first three months of marriage	9.2	[illegible]	5.8	8.3	3.5	4.9	10.1	13.8	16.0	10.4	10.7	5.1	100
Number of conceptions of primiparas in whom conception occurred after the three first months of marriage	90	75	86	125	74	89	97	98	81	86	160	107	1 16
Percentage of all primiparas with conception after the three first months f marriage	7.7	6.4	7.4	10.7	6.3	7.6	8.3	8.4	6.9	7.4	13.7	9.2	100

ble 43 *Monthly variations in births and expected dates for babies who died during th rinatal period*

dar months	I+II	III+IV	V+VI	VII+VIII	IX+X	XI+XII	To
of births of perinatal ths	51	48	51	37	44	52	283
rcentag of all perinatal aths	18.3	17.2	17.9	12.9	15.4	18.3	100
rcentage distribution of ths of the total series	14.4	18.7	19.3	18.3	15.0	14.3	100
mber of expected dates of inatal de ths	62	54	38	50	37	38	279
rcentag of all expected tes of perinatal deaths	22.2	19.4	13.6	17.9	13.3	13.6	100
rcentage distribution of ex cted dates of the total series	13.3	20.1	19.1	17.5	15.0	15.0	100

Table 44 *Monthly variations in births and expected dates for preterm infants (gestational age less than 38 weeks).*

Calendar months	I+II	III+IV	V+VI	VII+VIII	IX+X	XI+XII	Total
Number of births of preterm infants	197	177	206	155	156	144	1035
Percentage of all preterm infants	19.0	17.1	19.9	15.0	15.1	13.9	100.0
Percentage distribution of births of the total series	14.4	18.7	19.3	18.3	15.0	14.3	100.0
Number of expected dates of preterm infants	174	187	188	177	178	131	1035
Percentage of all expected dates of preterm infants	16.8	18.1	18.2	17.1	17.2	12.6	100.0
Percentage distribution of expected dates of the total series	13.3	20.1	19.1	17.5	15.0	15.0	100.0

Table 45 *Monthly variations in births and expected dates for postterm infants*

Calendar months	I+II	III+IV	V+VI	VII+VIII	IX+X	XI+XII	Total
Number of births of postterm infants	69	91	128	138	114	96	636
Percentage of all postterm infants	10.9	14.3	20.1	21.7	17.9	15.1	100.0
Percentage distribution of births of the total series	14.4	18.7	19.3	18.3	15.0	14.3	100.0
Number of expected dates of postterm infants	77	103	127	138	112	79	636
Percentage of all expected dates of postterm infants	12.1	16.2	20.0	21.7	17.6	12.4	100.0
Percentage distribution of expected dates of the total series	13.3	20.1	19.1	17.5	15.0	15.0	100.0

Table 46. *Monthly variations in births and expected dates fo low birth weight infants*

Calendar months	I+II	III+IV	V+VI	VII+VIII	IX+X	XI+XII	Total
Number of births of low birth weight Infants	94	92	88	73	74	78	499
Percentag of all low birth weight infants	18.9	18.5	17.6	14.6	14.8	15.6	100.0
Percentage distribution of births of the total series	14.4	18.7	19.3	18.3	15.0	14.3	100.0
Number of expected dates of low birth weight infants	92	88	85	86	68	67	486
Percentage of all expected dates of low birth weight infants	18.9	18.1	17.5	17.7	14.0	13.8	100.0
Percentage distribution of expected dates of the total series	13.3	20.1	19.1	17.5	15.0	15.0	100.0

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

161. Peltonen, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry*. Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W. Focal Spike Discharges in Children. A Longitudinal Study. Sw. kr. 35.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr 30.— 1966
170. Bellman, Margit, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Charanis*. Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr 15.— 1967
174. Petersen, Per Ove, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. [illegible], Fazel, Vectorcardiographic Studies in Newborn Infants. Sw. kr 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress*. Bergen. 1967 Sw. kr. 35.— 1967
178. Sjögren, Irène, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation*. Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968

Koch, Günter Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968

Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968

Robertson, Alan F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw kr. 25.— 1968

[illegible], Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968

Andersen, Else, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968

Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968

Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw kr. 30.— 1968

Meeuwisse, Gerard W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969

Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969

190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Kaivikko, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality 1969
194. Kasanen, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw kr. 20.— 1969
197 Sandin, Elva, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. [illegible], Dina M., Cravioto, Joaquin, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette E., Hartroft, Phyllis, Balis, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr, L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress*. Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr 35.— 1970
210. Rosberg, Georg, Parental Attitudes to Pediatric Hospital Admissions. Sw. kr 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Halvorsen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr 25.— 1971
214. Samuelson, Göran, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County I. Food Consumption Survey. Sw. kr. 25.— 1971
215. Berggren, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr 25.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217 *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium*, Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. Sw. kr. 35.— 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 35.— 1971

Price Swed. kr 35.—

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 220 1971

STUDIES ON GROWTH OF FINNISH CHILDREN FROM BIRTH TO TEN YEARS

BY NIILO HALLMAN LEENA BÄCKSTRÖM, RIITTA LIISA KANTERO AND RITVA TIISALA

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

Fig. 1 Mean height and limits of ± 1 SD of the longitudinal series of children ged 0—10 years dra n as heavier lines on the cross-sectional curves. (a) Boys. (b) Girls.

ts of ± 1 SD of the longitudinal series of children ged 0—10 years dra as hea er lines n the cross-sectional curves ( ) Boys. (b) Girls.

even course slightly above the compared curve, but the mean values differed by less than 1 SD At the age of ? the girls weighed on the average 12.5 ± 1.4 kg, which was approximately the same as the mean in the cross-sectional series. At age 10 their mean weight was 32.9 ± 5.5 kg, which already was 3 kg above the mean in the compared series. The curves for boys were already in infancy slightly above the corresponding curves in the comparison series. The mean weight at 2 years was 13.3 ± 1 6 kg, compared with 12.7 ± 1 4 kg in the cross-sectional study The difference became more definite at pre school age the curve of mean weights reached the 84th percentile curve at the age of 6—7 years, after which the weight growth up to age 10 had practically the same direction as the normal distance curves. At and after pre-school age the standard deviations were correspondingly greater Thus at the age of 10 the mean difference was already about 6 kg, the figures in the two series being 35 6 ± 7 4 kg and ?9.5 ± 3.5 kg, respectively

Discussion

Examination of the "normalcy of the longitudinal Model Child series showed that girls fitted quite well into the cross-sectional curves of the Healthy Child series. However already after infancy there was an even trend, on the average to somewhat greater height and weight. A similar trend was more evident in boys of school age with respect to height and already at pre school age with respect to weight.

In the present series the weight and height at birth of both boys and girls fell approximately into the 50th percentile initial point of the cross-sectional curves and they also correspond to the mean values reported in Finnish studies in the past decade with respect to birth weight (3 11) and to both (15) Although in the early 1930 s Ritala (1?) observed a clear increase from the values from the last century (7), the weight and height of Finnish babies have not increased at all during the last decades (15). The prenatal environment during the last two months of pregnancy has the most decisive influence on the size of the newborn child Only later in most cases not before infancy is over will the child s genetic growth potential and the mutual effect of certain external factors become growth-regulating factors. The generally accepted secular trend is considered to be a result of favourable external conditions that permit the individual to realize its growth potential (1 14)

The curves from the cross-sectional study are based on measurements made in the latter part of the 1950 s and the series of children measured can be regarded as representative of the whole of Finland (?) The longitudinal Model Child series, again, represents children born about 10 years later The tendency in this series to on the average, greater height and weight growths after infancy than those in the normal curves may possibly thus be a reflection of the secular trend, which is not yet seen in the birth height and weight. The fact that the secular trend is more clearly evident in boys than in girls in this series is probably due to the widely made observation that boys seem to be more sensitive than girls to growth-influencing external factors, even within physiological limits (1 14).

For practical reasons it was necessary to limit the present series primarily to children in the capital city (6) The cross-sectional study revealed that children in the southern part of Finland are bigger than those in the northern and eastern regions, the difference being more clearly evident in boys (13) In a detailed comparison of children in the capital city and those in a series of rural children the former were found to be at school age highly significantly taller and heavier (4).

As is stated in the introductory chapter of this supplement, the majority of the children in the present longitudinally studied series are Helsinki inhabitants of the first generation, i.e they were born in Helsinki but their parents were from different regions of Finland. Comparison of this series with the purely Helsinki series of Bäckström-Järvinen (4) shows great similarity of the results for girls. The boys in our series, on the other hand, were taller and heavier the

Fig. 1 Mean height and limits of ± 1 SD of the longitudinal series of children aged 0—10 years dra[illegible] as heavier lines on the cross-sectional curves. (a) Boys. (b) Girls.

Fig. [illegible] Me[illegible]ght and limit[illegible] of ± 1 SD of the longitud[illegible]nal series of children [illegible]ged 0—10 years dra[illegible]n as hea[illegible]er lines [illegible]n the cross-sect[illegible]onal curves. ([illegible]) Boys. (b) Girls.

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 220 1971

STUDIES ON GROWTH OF FINNISH CHILDREN FROM BIRTH TO TEN YEARS

BY NIILO HALLMAN LEENA BÄCKSTRÖM, RIITTA LIISA KANTERO AND RITVA TIISALA

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

From the Finnish Centre for Study in Child Growth and Development,
University of Helsinki

STUDIES ON GROWTH OF FINNISH CHILDREN FROM BIRTH TO TEN YEARS

NIILO HALLMAN M D
LEENA BACKSTRÖM M D
RIITTA LIISA KANTERO M D
RITVA TIISALA, M D

HELSINKI 1971

Translated by Miss Elvi Kaukokallio

This study was supported by grant
from the Ministry of Education.

Printed in Finland

[illegible] Oy Helsinki 1971

CONTENTS

I. Presentation of the Material
Niilo Hallman — 5

II. Cross-Sectional Studies of Height and Weight in Finnish Children Aged from Birth to 20 Years
Leena Bäckström and Riitta-Liisa Kantero — 9

III. Comparison of Height and Weight Distance Curves Based on Longitudinal and Cross-Sectional Series from Birth to 10 Years
Ritva Tiisala and Riitta Liisa Kantero — 13

IV Height, Weight and Sitting Height Increments for Children from Birth to 10 Years
Riitta Liisa Kantero and Ritva Tiisala — 18

V Growth of Head Circumference from Birth to 10 Years
Riitta Liisa Kantero and Ritva Tiisala — 27

VI. Predictability of Individual Height and Weight Growth from Cross-Sectional Distance Curves from Birth to 10 Years
Riitta Liisa Kantero Ritva Tiisala and Leena Bäckström — 33

VII. Some Parent-Child Correlations for Height, Weight and Skeletal Age up to 10 Years
Ritva Tiisla and Riitta Liisa Kantero — 42

Translated by M ss El I Kaukokallio

This study was supported by a grant
from the Ministry of Education.

Printed in Finland

Frenckellin Kirjapaino Oy Helsinki 1971

I Presentation of the Material

Niilo Hallman

A longitudinal study of child growth and development has been in progress in Finland since 1953. Details of the arrangement of the project were published in an earlier paper (1). The studies now being presented cover the first 10 years of life. Although it is needless in this connection to describe the material again, it is well to examine certain points that have a bearing on its representability.

The children's birth years are seen in Table 1. The greater part of the children were born between the years 1955 and 1960 inclusive. The original purpose was to observe the development of at least 100 children up to the end of the growth period, and it appears that this aim can be achieved. At the time of the present analysis

Table 1. *Distribution of observed children by year of birth*

Year of birth	1953	–54	–55	–56	–57	–58	–59	–60	–61	–62	–63	–64	–65	–66	–67	–68
Active participants	1	6	18	18	26	7	13	15	5	6	—		—	—	—	2
Discontinued	1	4	7	5	6	5	3	4	3	—	1	1	—	—	—	1

Total active participants	119
Total discontinued	41
	160

Table 2. *Children who have discontinued attendance*

Reasons for discontinuation	Number of children	Ages at time of discontinuation
Disinterest	18	1, 5, 6, 6, 6, 7, 8, 15, 15, 18, 24, 24, 30 months 3, 11, 11, 11, 13 years
Change of residence	13	2, 5, 5, 11, 12, 24, 30 months, 4, 4, 5, 6, 8, 12 years
Fear of X-ray examination	3	1, 12, 24 months
Illness		
Hydrocephalus	1	12 months
Acute leukemia, died	1	7 years 4 months
Congenital heart disease, died	1	9 day
Mental retardation – convulsions *)	1	4 years
Cerebral palsy – Dystrophia musc progr	1	7 years
Due to one child's illness *) the parents did not want their other two children to participate	2	4 and 6 years

Total 41 (= 25 per cent)

119 children were actively participating in the study while 41 children had discontinued for various reasons.

The reasons for discontinuation appear from Table 2. The main reason was loss of interest. It is to be noted that interest in the project wanes already during the first or the first two years. This is the same phenomenon as is seen also with respect to ordinary healthy children attending child welfare centres. Contacts with the growing child cannot be maintained at preschool age as well as previously If observation can be continued through this period, a second phase of disinterest occurs at early prepuberty In many of the cases in the latter instance it is most probably that the child becomes reluctant, whereas on the earlier occasion we can speak of disinterest on the part of the parents. It may be mentioned that the age of 11 is the time when children in Finland pass from primary school to secondary school and thus enter a different school and get new classmates.

Removal of the family to another locality is also an important reason. The families participating in the child growth study are naturally young, and in Finland migration to towns and especially to the capital city has been very active in recent years. Conversely there is also considerable migration to rural areas, where employment is available especially for skilled workmen and for students after completing their studies. It must be pointed out, however that a very notable part — a total of 10 — of the children who have changed residence, in some cases quite far from the place of examination, are continuing to attend the scheduled control examinations. Altogether 5 children do not live in the city of Helsinki

A further reason to be mentioned is the fear of X ray examinations. — Naturally the children who were chronically ill in some way 5 in total are not later included in this series of healthy children. Since in some cases the material includes more than one child from the same family it is understandable that the illness of one child led to abandoning of the project by other children, too.

In order to determine how well the now longitudinally studied material is representative of the Finnish child in general, despite the fact that the place of examinations is located in the capital city situated in the extreme south of the country information has been obtained on the place of birth of parents. Both parents were born in Helsinki in the case of 16 per cent of the children of the families participating in this growth study Of 9 per cent the mother only was born in Helsinki. This means that 75 per cent of the mothers came from other regions of Finland. Similarly only the father of 24 per cent of the children was born in Helsinki and so the capital was the place of birth altogether of fathers of 40 per cent of the children. The distance from Helsinki of the parents places of birth will be seen in Tables 3 and 4

Table 3 *Location of birthplaces of mother*

Helsinki	26
< 50 km from Helsinki	3
50—200 —»—	16
200—400 —»—	37
400—600 —»—	17
> 600 —»—	1
Total	100

Table 4 *Location of birthplaces of fathers*

Helsinki	40
50 km from Helsinki	1
50—200 —»—	19
200—400 —»—	23
400—600 —»—	15
> 600 —»—	2
Total	100

For greater clarity the graphs in Figs. 1 and 2 show the birthplaces of the mothers and the fathers. When we consider that about one half of the population of Finland lives in the southern one fourth of the country the studied series of children can be said to represent the whole Finnish population quite well when evaluated according to the birthplace of parents. Naturally however the migrated population differs from that remaining in the locality of their birth The better conditions prevailing in the new place of residence must also be taken into consideration. For this reason the material can nevertheless not be regarded a representative of the conditions in the whole country

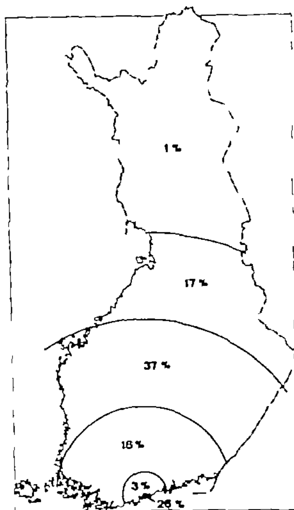


Fig. 1 Location of places of birth of the mothers.

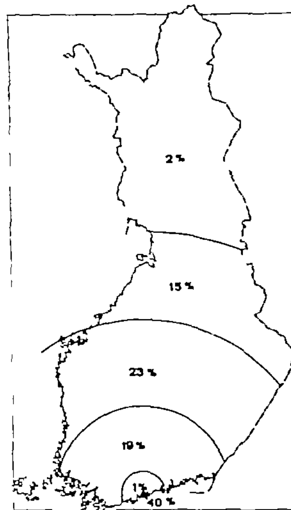


Fig. 2. Location of places of birth of the fathers.

At the time of the present analysis the places of residence of the children participating in the study are as follows

Helsinki or neighbouring communities	88 %
Less than 200 km from Helsinki	8 %
200—400 km from Helsinki	1.5 %
Over 400 km from Helsinki	2.5 %

The social status of the participating children, or rather of their families, has been analysed in detail in earlier reports. Almost without exception they are middle class families. An increasing number of mothers are employed outside the home. The distribution at this time is seen in Table 5 The proportion of this study's mothers occupied outside the home is exactly the same as that of mothers in Helsinki in general.

Table 5 *Mothers employed outside the home*

	At home	Outside the home
Mothers in the present series	29.0	71.0
Helsinki mothers in general, 1960—62	29.6	70.4

Table 6. *Maternal age at birth of observed child*

Age, years	Present series	Helsinki mothers, 1956—60
Under 20	5.3	4.6 %
20—25	42.1	29.0
25—30	29.5	31.8
30—35	16.8	21.0
35—40	2.1	10.5
Over 40	4.2	3.9

The maternal age at birth of the child (Table 6) corresponds fairly well with the general age distribution of parturients in Helsinki. It can be observed, however that the 20—25 year group in this study is greater than any of the older age groups. In part at least this is explained by the fact that a considerable proportion of the children are their parents' first born. Mothers who have given birth to several children are not as clearly interested in a study of this kind.

The studies now presented touch upon certain parameters that have bearing upon physical growth. No comparisons with psychic development are made in this connection. There may be reason to mention, however, that the distribution of gifted children within each age group in this study is of the same order as that in the general population.

Reference

1 *Hallman, N., Backström-Järvinen, L., Kantero, R.-L. & Tiisala, R.:* Finnish Centre for Study in Child Growth and Development. *Ann Paediat Fenn, 1* 8, 1964

II Cross-Sectional Studies of Height and Weight in Finnish Children Aged from Birth to 20 Years

LEENA BÄCKSTRÖM and RIITTA LIISA KANTERO

The child growth study in Finland includes, in addition to the longitudinal urban project, certain extensive cross sectional studies that are conducted from time to time (1 3, 8, 9 10). Fifteen localities are selected by statistical sampling from different parts of Finland to form a "miniature Finland" (9). The normal height and weight curves in use in Finland at the present time are based on these cross-sectional studies. The series of children, methods of examination and analysis of results have been described in detail in earlier papers (1 8). Since the curves were compiled from the data of two series examined partly in different studies and complementing each other there has appeared a need for tables showing the combined results. Such tables are necessary when deviating groups of children, e.g. children with dwarfism, congenital anomalies or other affections, are to be compared in growth with healthy children and the statistical significance of the differences is to be determined.

Material

Infants

In collecting the sample for the original Healthy Child study the intention was to obtain a statistically adequate sample of about 100 children for each sex and year of life. It is definitely clear, however, that during the first two years of life, the period of the most active growth, the measurements should be obtained at one-month intervals. Thus the sample for this period was too small. To fulfil this requirement Bäckström (1 7) collected a new series of infants. For practical reasons the sampling was limited to Helsinki and the series for study was collected from the health-cards of child welfare centres by systematic random sampling. The newborns were collected from the Department of Gynaecology and Obstetrics of the University Central Hospital, Helsinki. Infants whose birth weight was below 2,500 g were excluded from the series.

The size of each age groups of infants is seen in Tables 1 and 2. A total of 2,118 measurements of height and 2,164 of weight were made. Girls and boys were approximately equal in number in the infant series, and 82 2 per cent of the girls and 86 6 per cent of the boys were resident in Helsinki.

Children aged 2—20 years

The groups of children of pre-school age (2—6 years) was formed by combining the children of this age in the original Healthy Child study, totalling about 1,500, and the Helsinki series of about 500 children, also child welfare centres. Rural children are therefore more numerous in this age group than urban children. In the group of children of school age (7—15 years) the original series was supplemented with measurements obtained from the health-cards of elementary and secondary school pupils in Helsinki. The original rural series of school age totalled 2,13 children and the supplementary group 14,510 children. Thus 84 8 per cent of this group are urban children. The rural study included no children 16—20 years of age, and this age group in the present study was collected entirely by Bäckström-Järvinen (1). The groups 16, 17 and 18 years of age were formed by combining the series from Finnish-speaking and Swedish-speaking secondary schools. Since the number of 19- and 20-years-olds was of course small in these series, it was increased with a part of the same author's series of military conscripts and pupils in nursery schools. This addition was not large: 57 conscripts and 129 nursery school pupils. As far as possible they were selected according to the localities from which the sample for the Healthy Child study was originally taken.

In the total series 2—20 years of age 77 per cent of the girls and 84 8 per cent of the boys were residents of Helsinki. A total of about 8,600 girls and 8,900 boys were measured. The size of the material used in compiling the tables of children and young adults 0—20 years of age was about 9 600 girls and 9 900 boys, about four-fifths of whom were from Helsinki.

Table 1. *Height and weight means of boys aged 0—24 months*

Age in months	N	Height, cm Mean	SD	N	Weight, kg Mean	SD
0	100	51.0	2.0	100	3.6	0.3
1	45	55 0	2.[illegible]	42	4.2	0.4
2	52	58.2	2.4	54	5.1	0 6
3	56	61 2	2.4	55	6.[illegible]	0.8
4	60	64	[illegible].5	50	7.0	0.9
5	4[illegible]	66.6	2.7	41	7 7	1 0
6	60	68.4	2.7	58	8.3	1.0
7	52	70.2	2.9	43	8.8	1 1
8	55	71.8	2.9	52	9.2	1 1
9	56	73 0	2.8	53	9 6	1 1
10	48	74.[illegible]	2.8	48	9.8	1 1
11	45	75.2	2.9	42	10.2	1.[illegible]
12	112	76 5	[illegible].9	105	10.5	1 1
15	50	79.3	[illegible].7	96	11 1	1.2
18	6[illegible]	8[illegible].1	[illegible].9	52	11.6	1.2
21	96	85.0	3.4	64	12.[illegible]	1.3
[illegible]4	90	87.8	3.5	10[illegible]	12.7	1.4
Total	1081			1057		

Table 2. *Height and weight means of girls aged 0—24 months*

Age in months	N	Height, cm Mean	SD	N	Weight, kg Mean	SD
0	100	51.0	[illegible]	102	3 4	0.3
1	54	54 6	[illegible].1	56	3.9	0 3
2	48	57.9	[illegible].1	48	4 6	0.3
3	44	60.7	[illegible]	49	5 6	0.4
4	50	63 0	2.0	56	6.4	0 5
5	46	65.2	[illegible].3	62	7 1	0.6
6	58	67.0	2.4	60	7 7	0.7
7	46	68.8	[illegible].5	52	8.3	0 8
8	54	70 1	[illegible].5	49	8.7	0.9
9	50	71.5	[illegible].4	5[illegible]	9 1	1.0
10	48	72.8	2.6	55	9 4	1 1
11	48	74.0	[illegible].7	53	9 7	1 1
12	102	75.0	2.8	104	10.0	1 1
15	48	78 4	2.9	64	10.7	1.2
18	60	81.3	3.2	96	11 4	1.3
21	89	84 1	3.5	50	11 9	1 4
[illegible]4	92	86 8	3.5	99	12.5	1.5
Total	1037			1107		

Table 3. *Height and weight means of boys aged 2—20 years*

Age in years	N	Height, cm Mean	SD	N	Weight, kg Mean	SD
2	154	87.5	3 1	163	1[illegible].7	1.3
3	45	96.0	3.9	47	14.6	1 4
4	216	103.0	3.9	12	16.2	1 7
5	[illegible]08	109 1	4 4	204	17 7	1 9
6	[illegible]00	115.0	4.4	203	19.6	2.3
7	862	1[illegible]1.2	4.5	861	2[illegible].0	[illegible].7
8	911	127.0	4.5	910	[illegible]4.9	[illegible].9
9	1025	131.2	4.9	1025	[illegible]7.0	3.1
10	874	136.3	5.1	874	29.5	3.5
11	8[illegible]4	142.0	5.4	8[illegible]4	3[illegible].5	4.3
12	847	147 0	6.2	847	35 7	5.0
13	662	151 7	6 8	662	39.3	5.5
14	513	157.2	6.8	513	44 0	7.3
15	412	165 0	7.8	411	51.0	8.0
16	[illegible]76	172.5	7 1	278	59.2	5.7
17	[illegible]16	175 4	6.6	216	62.8	8.2
18	1[illegible]9	177 2	6 0	179	65 9	7.9
19	180	177.[illegible]	5 7	19[illegible]	67.0	8 0
20	9[illegible]	178.0	5.6	96	67 9	7.8
Total	[illegible]96			[illegible]917		

Table 4. *Height and weight means of girls aged [illegible]—20 years*

Age in years	N	Height, cm Mean	SD	N	Weight, kg Mean	SD
[illegible]	143	86 0	[illegible].7	148	12.2	1 3
3	40	93.7	3 1	257	13.9	1.5
4	209	101.0	3 6	[illegible]22	15.6	1.8
5	[illegible]12	107.9	3 9	181	17 4	1 9
6	201	113.7	4.5	204	19.2	[illegible].0
7	903	120.1	4.3	903	21 7	[illegible].5
8	925	125.0	4.5	925	24 0	3.1
9	1018	130.0	4 9	1018	26.8	3 6
10	885	135.2	5 4	884	29.2	4 1
11	675	141.0	6.2	674	32.6	5.6
12	725	147.0	6.6	724	36.3	6.5
13	613	153.2	7.3	613	41 1	7.6
14	497	158.5	6.5	497	47.0	7.5
15	396	162.0	6.3	396	51.2	7 7
16	310	164 5	5.7	310	54.4	7.6
17	233	164.8	5 0	233	55 6	7.2
18	196	165.1	5.0	198	56.6	6.9
19	152	165.1	5.0	155	57.0	6.5
20	102	165.1	5.0	101	57 1	6.3
Total	8635			8593		

Results

Infants

The means and standard deviations of the heights and weights of boys and girls are shown in Tables 1 and 2. The children are grouped by age in such manner that, for example, the group aged 3 months is comprised of children 2.5—3 5 months of age the mean age in the group thus being exactly [illegible] months According to the sample in the pr[illegible]nt study the mean birth height of the boys and girls was the same (51 0 cm), but boys were 200 g heavier than girls at birth (3 6 and 3 4 kg) At the age of 12 months there were differences of 1.5 cm in height and of 500 g in weight in favour of boys at 2 years these differences between the sexes dropped to 1 cm and back to 200 g.

Children aged 2—20 years

The results of the measurements of children

and young adults who have passed their second birthday are presented in Tables 3 and 4. It is noteworthy that in the 2 year-old group the means of both height and weight are slightly below those in Tables 1 and 2. This is because the earlier tables were consistently based on series of mainly urban children, whereas the data on pre-school children in Table 3 and 4 are from a series of mainly rural children, as said above. The normal curves in use in Finland have also been drawn separately and the same discrepancy appears also in them. As was stated by Bäckström-Järvinen (1), Helsinki children of all ages are on the average taller and heavier than rural children.

A general observation from Tables 3 and 4 is that with the increase in the mean heights and weights with age there also was an increase in SDs up to the age of 13 in girls and of 15 in boys, after which a decrease sets in. The mean height for girls no longer increased after age 17 while as late as at 20 years the mean height for boys was greater than at 19. The mean weight for both sexes increased up to age 20. A definite sex difference in height makes its appearance at age 16, when also the mean weights clearly differ for the first time.

According to the present study the mean height of the Finnish young man is 178.0 cm and of the young woman 165.1 cm.

Discussion

It has been demonstrated in earlier studies (1, 8) that the children in the rural areas of Finland are shorter in stature throughout their growth period and in adult height than the urban children in the capital city Helsinki. When the object is to obtain normal curves that would be applicable to the whole country the series should be so selected that the urban and rural populations are represented in the same proportion as in the total population of the country. In 1968 50.3 per cent of the population of Finland lived in cities, towns and market towns. Thus the proportion of urban children in all of the series used in the present study is too large. It might be expected that when the curves drawn on their basis are used, for instance, in the north-eastern regions of Finland, more than half of the measured values fit under the 50th percentile.

Owing to the lack of detailed information it is not possible to assess the exact amount of migrated population among these children who now go under the same of "the Helsinki series". It was impossible to investigate in each case whether the child was born in Helsinki or had moved there recently. It is known, however that the direction of the present migration of population is Helsinki: for example, 5.5 per cent of the present population of Helsinki had moved into the city in 1969. It may therefore be assumed that the assembled series is a representative sample of the Finnish child. Practical application of these growth curves in studies in various parts of Finland has shown them to be fairly suitable for the purpose (7).

It has also been shown in various connections that the secular trend continues in Finland (1, 8). Consequently the normal values become comparatively rapidly outdated. The mean height of children of school age has increased in 10 years by 1—2 cm (8). Nearly 10 years have now passed since the collection of the presented series and it therefore can be expected that at least in the case of urban children the majority will show a tendency to be over the 50th percentile. This fact will be demonstrated in the following paper (11).

In some earlier papers we compared the measurements of Finnish children with those published from other countries and found that the means were nearly the same as those in the United States, Switzerland and Sweden, and that they were higher than those of Polish, Russian or Italian children (1, 8).

It is not possible to determine from cross-sectional values the time at which children have their peak height velocity. Some cautious conclusions can be drawn, however indicating that the largest dispersion of height measurements is at the age of 13 for girls and 15 for boys.

The Finnish child's age at menarche was in 1969 13.16 years (4). The menarche follows fairly closely after PHV (5, 6, 12) and thus the greater part of the girls 13 years of age were in their most active growth phase; on the other hand the girls in this age group show great variation in their stage of development. The widest dispersion of the height measurements for boys occurs at the age of 15, i.e. two years later than for girls. This is well compatible with the observations in the literature that the PHV of boys always occurs later than that of girls (5, 6, 12). It is natural that the presented estimations of the commencement of puberty in both boys and girls with the aid of PHV must be accepted with a certain reservation because the series was collected by the cross-sectional method. Only after the longitudinal growth study of Finnish children is ultimately completed will it be possible to present data on the exact time of PHV in boys and girls.

Summary

The normal height and weight means and standard deviations of the Finnish child from birth to 20 years are presented, separately for boys and girls. The series was collected by the cross-sectional method and totalled about 9 600 girls and 9,900 boys, about four fifths of whom were residents of Helsinki.

The possibility to consider the used series representative of children in the whole of Finland is discussed. The error arising from the disproportionately large number of Helsinki children in the series is compensated by the migration to this city, owing to which some part of the urban children are of rural origin. The continuing secular growth will in the course of years reduce the validity of the presented measurements.

References

1. Bäckström-Järvinen, L. Heights and weights of Finnish children and young adults. *Ann Paediat Fenn. 10* Suppl. 23 1964.
2. Bäckström, L. Unpublished data.
3. Haataja, J. Cephalic, facial and dental growth in Finnish children. *Suomalaisen Hammaslääkäriseuran Toimituksia, 59* Suppl. *1* 1963.
4. Kantero, R. L. & Widholm, O. Age of menarche in Finnish girls in 1969. *Compte rendu de la X^e réunion des équipes chargées des études sur la croissance et le développement de l'enfant normal*, International Children's Centre, Paris 1970, Tome II.
5. Marshall, W. & Tanner, J. M. Variations in pattern of pubertal changes in girls. *Arch Dis Childh, 44*, 291 1969.
6. Marshall, W. & Tanner, J. M. Variations in the pattern of pubertal changes in boys. *Arch Dis Childh, 45* 13, 1970.
7. Palolampi, E. Studies on Finnish rural children, 1970. Unpublished data.
8. Takkunen, R. L. Anthropometric studies in Finnish children. *Ann Paediat Fenn, 8* Suppl. *19* 1962.
9. Takkunen, R. L., Tiisala, R., Bäckström-Järvinen, L. & Hallman, N. Health and development of Finnish children. *Ann. Paediat Fenn 10* Suppl. *4* 5 1964.
10. Tiisala, R., Takkunen, R. L., Bäckström-Järvinen, L., Kasala, E. & Hallman, N. General characteristics and health of Finnish children. *Ann Paediat Fenn 10* Suppl. *4* 19 1964.
11. Tiisala, R. & Kantero, R.-L. Comparison of height and weight distance curves based on longitudinal and cross-sectional series from birth to 10 years. *Acta Paediat Scand* Suppl. 220 13, 1971.
12. Wafelbakker, F. Adolescent growth spurt in relation to age and maturation. *Compte rendu de la X^e réunion des équipes chargées des études sur la croissance et le développement de l'enfant normal*, International Children Centre, Paris 1970, Tome II.

Key words: Height growth, weight growth

III Comparison of Height and Weight Distance Curves Based on Longitudinal and Cross-Sectional Series from Birth to 10 Years

RITVA TIISALA and RIITTA LIISA KANTERO

The object of the present work was to study how well the longitudinal Finnish "Model Child" series (6) fits the normal distance curves for height and weight based on a cross-sectional series of Finnish children (2). The examination of the "normalcy" of the series is important because the longitudinal data of the series will be used to describe the growth of the Finnish child in more detailed examinations and because growth velocity curves based on the results obtained will be presented for use in practical work (8, 9).

Material

The composition and examination program of the "Model Child" series ha been described in detail in an earlier paper (6). The present study includes 37 boy and 76 girls who ere examined at intervals of 3 months during the first two years of life and at 6-month intervals thereafter. The children ere measured and eighed by the same observers and according to the same principles as the children in the large cross-sectional "Healthy Child" series (2). At each age the mean alues and standard deviations ere calculated separately for boy and girls.

Results

Height

The dispersion of the measurements is shown by curves of the means and of 1 standard deviations (Figs. 1a, 1b, 2a and 2b). The mean height at birth was 50.6 ± 1.90 ¹) cm for boys and 50.3 ± 1.73 cm for girls. In the cross-sectional study these measurements were 51.0 ± 2.0 cm and 51.0 ± 2.2 cm, respectively the curves from birth to 24 [illegible] proximately similar to the cr[illegible] tance curves. Later in early chi[illegible] for both sexes were slightly ab[illegible] series used for comparison. Th[illegible] girls was still at age 2 on the [illegible] longitudinal and the cross-sec[illegible] later this difference for girls [illegible] evently within 1 SD. Thus at [illegible] in height was 3.6 cm in [illegible] tudinal series, the heig[illegible] 138.8 ± 5.8 cm and 135.2 [illegible] height of boys reached [illegible] of 8 to 10 years the 84th [illegible] limits lay quite close t[illegible] percentiles. The increa[illegible] cy between the mean [illegible] longitudinal series and [illegible] tional series is shown by [illegible] The mean values at 2 [illegible] agreement (88.2 ± 3.6 [illegible] at age 10 the differen[illegible] 5 cm (141.0 ± 6.3 [illegible] respectively).

Weight

The mean birth [illegible] bx [illegible] and 3.51 ± [illegible] sectional series [illegible] and 3.42 ± 0.4 kg [illegible] girls from birth to [illegible] completely with [illegible] Later in infancy [illegible]

¹) Mean ± SD

Fig. 1 Mean height and limits of ± 1 SD of the longitudinal series of children aged 0—10 years drawn as heavier lines on the cross-sectional curves. (a) Boys. (b) Girls.

Fig. 2 Mean ... and limits of ± 1 SD of the longitudinal series of children aged 0—10 years drawn as heavier lines on the cross-sectional curves. (a) Boys. (b) Girls.

even course slightly above the compared curve, but the mean values differed by less than 1 SD. At the age of 2 the girls weighed on the average 12.5 ± 1.4 kg, which was approximately the same as the mean in the cross-sectional series. At age 10 their mean weight was 32.9 ± 5.5 kg, which already was 3 kg above the mean in the compared series. The curves for boys were already in infancy slightly above the corresponding curves in the comparison series. The mean weight at ? years was 13.3 ± 1.6 kg, compared with 12.7 ± 1.4 kg in the cross-sectional study. The difference became more definite at pre-school age: the curve of mean weights reached the 84th percentile curve at the age of 6—7 years, after which the weight growth up to age 10 had practically the same direction as the normal distance curves. At and after pre-school age the standard deviations were correspondingly greater. Thus at the age of 10 the mean difference was already about 6 kg, the figures in the two series being 35.6 ± 7.4 kg and ?9.5 ± 3.5 kg, respectively.

Discussion

Examination of the "normalcy" of the longitudinal "Model Child" series showed that girls fitted quite well into the cross-sectional curves of the "Healthy Child" series. However already after infancy there was an even trend, on the average, to somewhat greater height and weight. A similar trend was more evident in boys of school age with respect to height and already at pre-school age with respect to weight.

In the present series the weight and height at birth of both boys and girls fell approximately into the 50th percentile initial point of the cross-sectional curves and they also correspond to the mean values reported in Finnish studies in the past decade with respect to birth weight (3, 11) and to both (15). Although in the early 1930's Ritala (1) observed a clear increase from the values from the last century (7), the weight and height of Finnish babies have not increased at all during the last decades (15). The prenatal environment during the last two months of pregnancy has the most decisive influence on the size of the newborn child. Only later, in most cases not before infancy is over, will the child's genetic growth potential and the mutual effect of certain external factors become growth regulating factors. The generally accepted secular trend is considered to be a result of favourable external conditions that permit the individual to realize its growth potential (1, 14).

The curves from the cross-sectional study are based on measurements made in the latter part of the 1950's and the series of children measured can be regarded as representative of the whole of Finland ( ). The longitudinal "Model Child" series, again, represents children born about 10 years later. The tendency in this series to, on the average, greater height and weight growths after infancy than those in the normal curves may possibly thus be a reflection of the secular trend, which is not yet seen in the birth height and weight. The fact that the secular trend is more clearly evident in boys than in girls in this series is probably due to the widely made observation that boys seem to be more sensitive than girls to growth-influencing external factors, even within physiological limits (1, 14).

For practical reasons it was necessary to limit the present series primarily to children in the capital city (6). The cross-sectional study revealed that children in the southern part of Finland are bigger than those in the northern and eastern regions, the difference being more clearly evident in boys (13). In a detailed comparison of children in the capital city and those in a series of rural children the former were found to be at school age highly significantly taller and heavier (4).

As is stated in the introductory chapter of this supplement, the majority of the children in the present longitudinally studied series are Helsinki inhabitants of the first generation, i.e. they were born in Helsinki but their parents were from different regions of Finland. Comparison of this series with the purely Helsinki series of Bäckström-Järvinen (4) shows great similarity of the results for girls. The boys in our series, on the other hand, were taller and heavier the

Fig. 1. Mean height and limits of ± 1 SD of the longitudinal series of children aged 0—10 years drawn as heavier lines on the cross-sectional curves. (a) Boys. (b) Girls.

Fig. 2. Mean weight and limits of ± 1 SD of the longitudinal series of children aged 0—10 years drawn as heavier lines on the cross-sectional curves. (a) Boys. (b) Girls.

Part III Physical growth during the first three years of life. *A ta Paediat Scand, 58* Suppl. *187* 48, 1968.

11 Raatakallio, P G oups at risk in low birth eight infants and perinatal mortality *Acta Paediat Scand,* Suppl. *193* 1969

12. Ruiala, A. M. Über die anthropologischen Messe der finnischen Neugeborenen. *Duodecim B, 16* 7 1931

13. T kkunen, R. L. Anthropometric studies of Finnish children *Ann Paediat F nn 8* Suppl. *19* 196..

14 Tanner J M *Growth at Adolescence* Blackwell Scientific Publications, Oxford 1964

15 Timonen, S Uoula, U Kuusisto, P Vara, P & Lok ki, O Effect of certain maternal foetal and geographical factors on the eight and length of the newborn nd on the dur tion of pregnancy *Ann Chir G naec F nn 55* 196, 1966.

Key words Height growth, weight growth

IV Height, Weight and Sitting Height Increments for Children from Birth to 10 Years

A mixed longitudinal stud

RIITTA LIISA KANTERO and RITVA TIISALA

When a child's physical growth is being assessed for the purpose of finding out whether or not the child's size is within normal limits it is sufficient to have the distance growth curves in which the normal dispersions are stated as either standard deviations or percentiles. On the other hand, in situations in which a child's development is to be followed episodically for example during a prolonged illness or a post illness condition, growth velocity curves are needed that show the normal dispersion of the growth increments. These standards are only obtainable from a longitudinally studied child series. The object of the present paper i to present data on the growth velocity of the Finnish child from birth to 10 years with respect to height, weight and sitting height.

Material and Methods

In the longitudinally followed series (L) regular measurements had been taken from birth to 10 years of 74 children — 3 boys and 4 girls — by the end of 1969. The total series included 57 boys and 76 girls, i.e., 133 children. Owing to occasional absences from examination and because of later inclusion of children in the series since birth, the number of children decreases after the age of 5 years, as is seen, for example, in Table 1. The children ere measured from birth to years at intervals of 3 months (± 7 days during 0—1 year and ± 14 days during 1— years), and thereafter at 6 months (± 14 days). The principles and instruments used in the measurements (5) were the same throughout the study and all measurements, with a few exceptions, ere made by the same person. After the ge of 21 months the children ere measured standing erect prior to this they were lying down.

The results of measurements were entered on punch-cards, control punched and handled by data machine at the Computing Centre of the Uni ersity of Helsinki. Only the measurements made t the right time were included. If one intervening measurement a missing among the observations, straight line interpolation w s performed on the data machine. The number of interpolated observ tions is listed in T ble 1.

T ble 1. *Interpolated inc increment alues per ent*

	Boys	Girls	Total
Height	6.8	6.6	6.7
Weight	7.4	6.4	6.8
Sitting height	17.0	17.8	17.5

To find the percentiles the increments ere listed. On their basis were sought certain ranges ithin which the results ppeared to fit. The data machine as then programmed to calculate the percentages of observations that fell into these anges. The object to find the alues below which 10 , 50 and 90 of the increments remained.

Results

Tables a and 2b present the *height* increments for boys and girls measured during the first 2 years at 3-month intervals and later at 6-month intervals. The columns on the right show the growth velocity per year during the respective age interval, calculated by multiplying the obtained 10th, 50th and 90th percentile values in the first 2 years of life by 4 and later by 2.

The growth velocity was great during the first two 3-month periods in boys the 50th percentile values were 45 cm/year and 8 cm/year and in girls 39 cm/year and 7 cm/year. The velocity decreased rapidly and at the beginning of the second year of life it was of the order of 11 cm/year. After the age of 5 years the growth

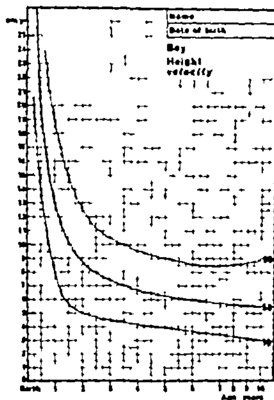
Table 2a. *Height increments and velocity percentiles for boys*

Age interval	Measured growth, cm			Growth velocity cm/year		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	55	12.0	3.8	36.0	44.8	[illegible]
3–6 months	55	8.2	4.4	20.7	28.0	[illegible]
6–9	55	4.4	1.2	12.0	16.0	[illegible]
9–12	55	3.7	1.1	9.2	14.4	[illegible]
12–15	55	3.1	1.2	5.6	11.2	[illegible]
15–18	52	2.8	1.2	4.4	10.4	[illegible]
18–21	52	2.4	1.0	4.0	9.6	[illegible]
21–24	51	[illegible]	1.4	4.0	8.4	[illegible]
2–2.5 years	53	4.5	1.5	5.0	8.8	[illegible]
2.5–3	51	5.3	1.1	4.4	7.6	[illegible]
3–3.5	50	3.9	1.1	4.6	7.6	[illegible]
3.5–4	51	4.2	1.7	4.0	7.5	[illegible]
4–4.5	54	3.5	1.0	4.0	6.6	[illegible]
4.5–5	53	3.7	0.8	4.8	7.0	[illegible]
5–5.5	53	[illegible]	0.7	4.1	6.0	[illegible]
5.5–6	51	3.3	0.8	4.2	6.5	[illegible]
6–6.5	46	3.2	0.8	4.0	6.2	[illegible]
6.5–7	43	3.1	0.9	3.8	6.0	[illegible]
7–7.5	41	3.1	1.2	3.5	5.4	[illegible]
7.5–8	41	3.9	1.8	3.7	5.8	[illegible]
8–8.5	39	3.0	0.9	3.4	5.8	[illegible]
8.5–9	36	2.7	0.9	2.7	5.4	[illegible]
9–9.5	30	2.7	1.2	2.0	5.3	[illegible]
9.5–10	32	2.5	0.7	3.1	4.8	[illegible]

Table 2b. *Height increments and velocity percentiles for girls*

Age interval	Measured growth, cm			Growth velocity [illegible]		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	74	10.1	1.6	36.0	[illegible]	[illegible]
3–6 months	72	7.2	1.5	21.0	[illegible]	[illegible]
6–9	72	4.7	2.8	10.0	[illegible]	[illegible]
9–12	72	3.9	1.3	8.0	[illegible]	[illegible]
12–15	74	3.1	1.1	5.6	[illegible]	[illegible]
15–18	72	3.2	1.2	5.6	[illegible]	[illegible]
18–21	70	2.4	1.3	4.0	[illegible]	[illegible]
21–24	69	2.5	1.2	4.8	[illegible]	[illegible]
2–2.5 years	70	4.3	1.0	6.0	[illegible]	[illegible]
2.5–3	73	4.2	1.1	5.0	[illegible]	[illegible]
3–3.5	71	3.7	1.3	4.4	[illegible]	[illegible]
3.5–4	71	4.7	1.1	4.1		[illegible]
4–4.5	71	4.8	1.1	4.2	[illegible]	[illegible]
4.5–5	71	3.7	0.8	5.0	[illegible]	[illegible]
5–5.5	68	3.4	1.0	4.0	[illegible]	[illegible]
5.5–6	68	3.2	1.1	3.8	[illegible]	[illegible]
6–6.5	64	3.2	1.1	4.0	[illegible]	[illegible]
6.5–7	63	3.2	1.6	4.0	[illegible]	[illegible]
7–7.5	60	3.1	1.2	3.4	[illegible]	[illegible]
7.5–8	58	2.9	1.0	3.5	[illegible]	[illegible]
8–8.5	51	2.7	0.9	2.2	[illegible]	[illegible]
8.5–9	47	2.8	0.9	3.3	[illegible]	[illegible]
9–9.5	43	3.0	1.0	1.4	[illegible]	
9.5–10	42	2.4	0.8	2.1	[illegible]	

[illegible]



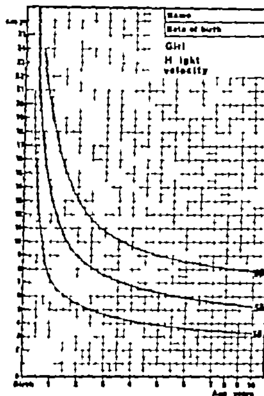
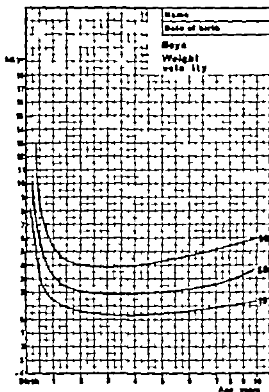


Fig. 1. Velocity curves of height for children aged from birth to ten years. (a) Boys. (b) Girls.



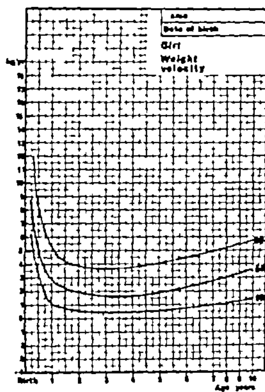


Fig. 2. Velocity curves of weight for children aged from birth to ten years. (a) Boys. (b) Girls.

Table 3a. *Weight increments and velocity percentiles for boys*

Age interval	Measured growth, kg			Growth velocity kg/year		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	55	[illegible]	0.56	8.14	10.30	13.80
3—6 months	55	[illegible]	0.65	6.36	9.44	12.50
6—9	54	1.29	0.49	2.26	[illegible]	7.56
9—12	54	0.88	0.41	1.38	3.37	5.66
12—15	52	0.74	0.47	1.25	2.77	5.41
15—18	49	0.78	0.43	1.20	2.76	5.00
18—21	47	0.59	0.36	0.60	2.16	3.64
21—24	49	0.65	0.46	0.72	[illegible]	5.00
2—2.5 years	48	0.89	0.55	0.40	1.65	2.80
2.5—3	49	1.04	0.65	0.20	2.00	4.50
3—3.5	49	1.19	0.72	0.64	1.96	4.40
3.5—4	47	[illegible]	0.77	1.00	2.10	4.00
4—4.5	51	1.19	0.87	0.62	1.80	5.00
4.5—5	48	1.30	1.00	0.20	2.10	5.00
5—5.5	48	1.29	0.89	0.76	2.34	4.00
5.5—6	49	1.26	0.78	0.76	2.00	4.00
6—6.5	46	1.55	0.90	0.84	2.92	4.90
6.5—7	43	1.43	0.99	0.86	2.36	4.66
7—7.5	42	1.60	0.75	1.34	3.00	5.00
7.5—8	39	1.41	0.73	1.00	2.62	4.80
8—8.5	38	1.82	0.97	1.32	3.28	5.60
8.5—9	36	2.09	1.11	2.00	3.76	6.00
9—9.5	31	1.96	1.12	1.00	3.90	6.50
9.5—10	32	1.88	1.25	1.20	3.33	6.50

Table 3b. *Weight increments and velocity percentiles for girls*

Age interval	Measured growth, kg			Growth velocity kg/year		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	75	[illegible]	0.49	6.16	8.88	11.00
3—6 months	75	2.04	0.54	5.75	7.92	11.90
6—9	73	1.30	0.57	[illegible]	4.89	8.00
9—12	[illegible]	0.81	0.38	1.00	3.12	5.12
12—15	69	0.72	0.36	[illegible]	2.67	4.79
15—18	69	0.71	0.40	0.76	[illegible]	5.00
18—21	65	0.62	0.35	0.60	2.16	4.44
21—24	68	0.73	0.41	1.00	[illegible]	5.00
2—2.5 years	70	0.93	0.50	0.50	1.76	3.00
2.5—3	73	1.01	0.59	0.50	1.74	3.50
3—3.5	70	1.17	0.79	0.64	1.90	4.00
3.5—4	60	0.93	0.59	0.54	1.86	4.18
4—4.5	65	1.19	0.65	1.84	1.96	4.00
4.5—5	65	1.16	0.86	[illegible]	2.00	4.00
5—5.5	67	1.31	0.79	1.00	[illegible]	4.42
5.5—6	66	1.26	0.88	0.70	1.99	5.00
6—6.5	64	1.35	0.80	1.00	2.36	5.00
6.5—7	59	1.41	0.82	0.88	[illegible]	4.74
7—7.5	57	1.33	0.61	1.00	[illegible]	4.41
7.5—8	57	1.46	0.97	0.86	[illegible]	5.00
8—8.5	48	1.99	[illegible]	1.30	3.50	6.00
8.5—9	44	1.79	1.41	0.80	[illegible]	4.80
9—9.5	40	1.69	0.92	1.00	3.22	5.50
9.5—10	41	[illegible]	[illegible]	1.18	3.08	5.40

T ble 4a. *Sitting he ght inc ement and locity per entiles for boys*

Age interval	Measured growth, cm			Growth velocity cm/year		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	34	8 3	..7	19..	32.0	40 0
3—6 months	44	4 0	3 0	..4	14 0	?9 0
6—9	45	..6	1.3	2 8	13 9	31 0
9—12	45	..3	2 8	0 2	6 0	17 0
1 —15	42	1 6	1..	0.5	5	11.2
15—18	33	1 5	1 1	0 5	4 1	11.2
18— 1	38	1.3	1 1	0 8	3 8	1..0
1— 4	37	1 2	0 8	0 5	4 0	11..
~..5 years	41	1 6	0 9	1 0	2.9	5 6
..5—3	40	1 4	0 6	0 8	..6	4.3
3—3 5	47	1 7	0 8	1..	3 0	6 4
3.5—4	43	1.5	1 0	0.4	2.6	5 4
4—4.5	48	1.5	1.3	0 2	2.4	5.5
4.5—5	48	1 5	1 1	1 0	2.5	5 4
5—5.5	41	1 5	0 9	1 0	2.8	5 0
5.5—6	45	1 7	0 9	1.3	3 0	5 0
6—6 5	42	1 4	0 6	0 5	..4	5 6
6 5—7	40	1 6	0 9	1	2.7	5 7
7—7.5	37	1..	1 0	0..	2.8	5 0
7.5—8	36	1 4	1 1	0 4	2.4	4 6
8—8 5	?9	1 4	0 9	0 8	2.3	4 7
8.5—9	28	1.8	1.2	0 4	2.2	7.0
9—9.5	20	1 0	0 8	0.7	1.2	5 0
9.5—10	..6	1..	0 9	0 6	1 7	5.5

Table 4b. *Sitting height increments and locity percentiles for girls*

Age interval	Measured growth, cm			Growth elocity cm/year		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	40	6 8	..1	13 6	..8	38 0
3 6 months	52	5 0	3 6	8 0	18.2	28 0
6—9	50	3 1	2 6	2 0	16 0	..4 0
9 12	45	..3	2.7	0	4 6	14 0
' 15	50	1 5	1 3	0	4 6	10 4
5 18	49	1.5	1 1	0	5..	10 0
8 1	39	1 2	1 5	0	3 0	10 0
4	48	1 4	1 4	0 4	4.2	10 8
	53	1 8	1 2	1 0	..8	7 4
	56	1 5	1.2	0	2.7	6 2
	1	1 4	0 8	0.7	2.4	6 2
		1 4	0 9	0 4	2.6	5 4
4 4		1 7	1 2	0 8	2 8	6.6
4 5		1 6	1 0	1.0	3.0	4 8
5 5		1 8	1 2	0.7	3 0	7.0
5 6		1 5	0 9	1 0	2.9	5.3
6 6 5		1	1 0	0.2	2.2	5.2
6 5 7	4	1	0 9	0.5	2.7	5 6
7 7 5	41	6	0 9	1 1	2 8	5.4
7 5 8	u	1	1 1	0.8	2.6	6.0
8 8 5	3	1	0 8	0 5	2.1	4 0
8 5—9		4	1 0	0 4	..4	5 0
9—9 5		4	1 1	0 8	..1	5.2
9 5—10	49	1	0 8	0 9	1 4	5.5

velocity declined to less than 7 cm/year for both boys and girls. Up to the age of 10 the growth velocity was nearly the same for both sexes, at a mean of slightly over 5 cm/year. With the decreasing growth velocity the dispersion of values also diminished. Among children of school age the 10th percentile of annual growth appeared to be of the order of 3 cm and the 90th percentile 8 cm. To make the results more comprehensible they are presented also as velocity curves, in the preparation of which the small variations presumably due to the smallness of the series have been levelled out (Figs. 1a and 1b).

The *weight* increments are shown in Tables 3a and 3b according to the same principles. The weight growth during the first 3 months was close to a velocity of 10 kg/year. Thereafter it rapidly decreased so that already at the beginning of the second year of life the velocities for both sexes had dropped to below 3 kg/year. Between the ages of 2 and 8 years the annual net growth was on the average about 2 kg, but then began to rise to over 3 kg for both girls and boys. The 10th percentile values after infancy were ½—1 kg/year. To facilitate the observation of individual development of a child the weight growth velocity is also presented in the form of curves in Figs. 2a and 2b.

The *sitting height* increments, separately for boys and girls, are presented in Tables 4a and 4b. In the first 3 months of life this increment accounted for more than a half of the total height increment, i.e., the child's height increases in this period mainly by growth of the trunk. Later however the sitting height increment appears to decrease in relation to the total height, so that during the observation years it is definitely less than a half of the total height increment expressed as absolute values. The lower limits seem at times to be close to zero but generally lie in the range 0.5—1.3 cm/year. The sitting height of the most actively growing children may episodically increase by 4.6—6.0 cm per year, i.e., by as much as the average total height growth per year of the other children. Although observation of the growth

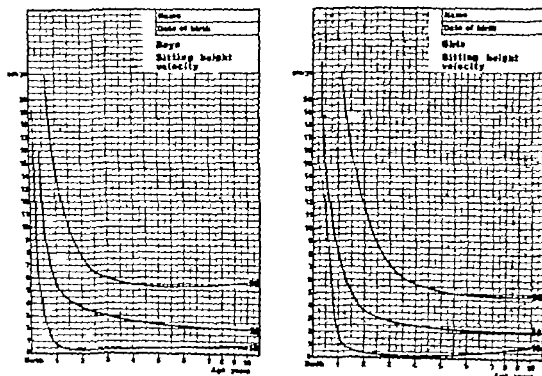


Fig. 3. Velocity curves of sitting height for children aged from birth to ten years. (a) Boys, (b) Girls.

velocity of the sitting height before puberty is seldom called for in practical work, these veloc ity curves also are presented for the sake of uniformity in Figs. 3a and 3b.

Discussion

Evaluation of the results is difficult because of the small number of comparable studies. Data from the co-ordinated international child growth study are available for only the first years of life (1 3). Because of the secular trend we do not consider it advisable to compare our results with those of studies made more than 20 years ago as for example the investigation of Reed & Stuart (4)

Height The growth increments during the first 3 years can be compared with the values measured from Swedish (3) and English (1) children, Table 5

The results obtained in the three countries can be considered to show good correspondence. No definite trend can be seen in the differences small differences are probably irregularities due to the smallness of these series. All the three series reveal that the height increment even in absolute mea ured values during the first 3 months is greater than the growth during the entire 12 months at the age of 3 years and nearly as great as at 2 years.

The growth velocity in centimetres per year during the entire growth period now under study can be compared with the results of the Harpenden growth study published by Tanner *et al* (6), Table 6 The re ults are almost identical Only in some [illegible] s during the first year of life there are differences of up to more than 2 cm, but later they are not more than a few millimetres.

Weight The comparison of weight of the children is limited to the same comparative materials, Table 7

A comparison of the means shows good agreement of the results. No tendency to differ is seen during the first 36 months. In the 3–6 months interval the Finnish boys increased in weight half a kilogramme more than the Swedish

Table 6. Height velocities of British and Finnish children

Age, year	50th centile cm/year Boys British children	Boys Present series	Girls British children	Girls Present series
0.16	40.00	44.8	34.00	39
0.37	30.00	28.0	26.00	27.0
0.6	18.00	16.0	19.00	16.0
0.87	14.50	14.4	15.90	14.8
1.1	1 30	11	13.50	11.6
1.37	11.10	10.4	11.30	1 0
1.6	9.90	9.6	10.60	8.4
1.87	9.70	8.4	9.60	9.6
.5	8.60	8.8	8.70	8.0
.75	8.0	7.6	8.1	8.4
3.5	7.60	7.6	7.64	7
3.75	7.16	7.5	7.—	7.0
4.5	6.84	6.6	6.84	6.8
4.75	6.60	7.0	6.60	7.0
5.5	6.36	6.0	6.36	6.6
5 5	6.18	6.5	6.18	6.4
6 5	6.00	6.	6.00	6.3
6.75	5.84	6.0	5.84	5.4
7.5	5.74	5.4	5.7	5.4
7.75	5.60	5.8	5.59	5.5
8 5	5.50	5.8	5.43	5.3
8.75	5.40	5.4	5.37	5.4
9.5	5.30	5.3	5.37	5.7
9 5	5.70	4.8	5.48	4.7

Height increment ... m in English, Swedish and Finnish children

Age interval	B	English children	Swedish children Boys	Swedish children Girls	Present series Boys	Present series Girls
0–3 months		6	10.5	9.8	1 0	10.1
3–6			6.6	6.5	8	7
6–9			4.5	4.8	4.4	4.7
9–1			4.0	4.1	3.7	3.9
1 –18			1		5.9	6.3
18–4			5.5	5.7	4.7	4.9
4–36	8.4		8.7	8.5	9.8	8.5

Table 7 *Means of weight increments in English, Swedish and Finnish children, kg*

Age interval	*English children*		*Swedish children*		*Present series*	
	Boys	Girls	Boys	Girls	Boys	Girls
0—3 months	—	—	2.34	2.18	2.65	2.19
3—6	2.01	2.05	1.89	1.87	2.40	2.04
6—9	1.45	1.30	1.37	1.44	1.29	1.30
9—12	0.86	0.93	1.10	1.00	0.88	0.81
12—18	1.32	1.24	1.56	1.39	1.52	1.43
18—24	1.08	1.06	1.13	1.19	1.24	1.35
24—36	1.96	2.08	1.98	2.16	1.93	1.94

boys, but later the weight increment did not exceed that of the latter. These series are nearly identical with respect to birth weight and length (3, 7), which therefore does not provide an explanation for this observation. Presumably a difference in feeding plays a part in this difference in weight increments, but in the lack of evidence this cannot be proved.

Table 8. *Whole-year velocities of weight of British and Finnish children*

	50th centile, kg/year			
	Boys		*Girls*	
Age, years	British children	Present series	British children	Present series
0.10	9.30	—	8.00	—
0.16	—	10.3	—	8.88
0.25	9.85	—	9.25	—
0.37	—	9.44	—	7.9
0.50	6.80	—	6.60	—
0.62	—	5.21	—	4.89
0.75	4.30	—	4.29	—
0.87	—	3.37	—	3.1
1.00	3.33	—	3.3	—
1.12	—	2.77	—	2.67
1.25	2.81	—	81	—
1.37	—	2.76	—	2.64
1.50	2.44	—	2.44	—
1.62	—	2.16	—	2.16
1.75	2.23	—	2.20	—
1.87	—	2.32	—	2.32
2.25	1.98	1.64	2.03	1.76
2.75	1.9	00	2.00	1.74
3.25	1.90	1.96	2.00	1.90
3.75	1.90	2.10	2.00	1.86
4.25	1.90	1.80	2.00	1.96
4.75	1.90	2.10	2.03	2.00
5.25	1.94	2.34	2.08	2.28
5.75	02	2.00	14	1.98
6.25	2.11	2.92	2.21	2.36
6.75	1	2.36	2.28	2.56
7.25	31	3.00	2.33	2.50
7.75	2.4	2.62	2.40	2.50
8.25	52	3.28	2.50	3.50
8.75	6	3.76	2.61	56
9.25	72	3.90	76	3.2
9.75	83	3.33	2.98	3.08

The weight growth velocity is compared in Table 8 with that of the British children. However, the age intervals used by Tanner differ from ours during the first two years of life and the data are therefore not directly comparable. Both series show nevertheless a similar downward trend in velocity. At a later age, from 7 years upwards, the Finnish boys included in this series appear to have a tendency to greater annual weight growth than British boys. Thus there is a difference of over 1 kg in favour of Finnish boys in the age intervals 8.5—9 and 9—9.5 years. The trend is not as evident in girls, but a few values are slightly higher than in the British series on approaching the age of 10.

With regard to the *sitting height* a comparison is possible with only the Swedish series (3), which is limited to the first 3 years, Table 9.

Also here the great similarity of the results is observed. There might be a suggestion of slight tendency to higher values for Finnish children.

To summarize the results of the comparison, it is observed that the results obtained for the Finnish children are practically the same through-

Table 9 *Increments of crown-rump length in Swedish and Finnish children, cm*

Age interval	Swedish children		Present series	
	Boys	Girls	Boys	Girls
0—3 months	—	—	8.3	6.8
1—3	4.7	4.4	—	—
3—6	3.8	3.7	4.0	5.0
6—9	2.3	3	2.6	3.1
9—12	1.8	1	2.3	3
12—18	3.2	3.1	3.1	3.0
18—24	1	2.1	5	2.6
24—36	3.4	3.2	3.0	3.3

out a th se for British and Swedish children with respect to those age intervals when the measurements were made at the corresponding times and when a comparison therefore is possible. The ranges of normal growth velocity are important to know when children's growth disturbances are being observed episodically. On the basis of the results presented here the normal values vary over a wide range and the limits of the 10th, 50th and 90th percentiles are mainly orientative. At the same time it has been found that the available British velocity curves are applicable also to the Finnish child during at least the first 10 years of life.

Summary

In a longitudinally followed series of 133 Finnish children the height, weight and sitting height increments were calculated during the first 10 years of life, at first at 3-month intervals and from the age of 2 years upwards at 6-month intervals. The results are stated as the means and standard deviations. On the basis of these results were sought the 10th, 50th and 90th percentiles of annual growth velocity which are expressed also in the form of curves. The results are compared with those obtained in recent series of British and Swedish children. A close correspondence of the results was observed.

References

1. F lkner, F. Some physical measurements in the first three years of life. Arch Dis Childh 33: 1, 1958.
2. Hallman, N., Backström-Järvinen, L., Kantero, R.-L. & Tiisala, R.: Finnish Centre for Study in Child Growth and Development. Ann Paediat Fenn 12: 8, 1966.
3. Karlberg, P., Engström, I., Lichtenstein, H. & Svennberg, I.: The development of children in a Swedish urban community. A prospective longitudinal study. Part III. Physical growth during the first three years of life. Acta Paediat Scand Suppl 187: 48, 1968.
4. Reed, R. B. & Stuart, H. C.: Patterns of growth in height and weight from birth to eighteen years of age. Pediat 24: 904, 1959.
5. Tiisala, R.: Anthropometric studies on Finnish children. Ann Paediat Fenn 5, Suppl 19, 196[illegible].
6. Tanner, J. M., Whitehouse, R. H. & Takaishi, M.: Standards from birth to maturity for height, weight, height velocity and weight velocity: British Children 1965. Part I and II. Arch Dis Childh 41: 454 & 613, 1966.
7. Tiisala, R. & Kantero, R.-L.: Comparison of height and weight distance curves based on longitudinal and cross-sectional series from birth to 10 years. Acta Paediat Scand Suppl 220: 13, 1971.

Key words: Height growth, weight growth, sitting height growth, growth velocity, growth increment

V Growth of Head Circumference from Birth to 10 Years

A mixed longitudinal study

RIITTA-LIISA KANTERO and RITVA TIISALA

A knowledge of the normal growth of the head circumference and its variations belongs to practical paediatrics in particular. The head circumference is also an anthropological dimension which varies for children of different nations. The same standards are therefore not applicable in all countries. They must be compiled specifically in the growth environment to which the child under examination belongs. For this reason, measurement of the head circumference has always been included in the Finnish study of child growth. Head circumference, as the other anthropometric dimensions, has a strong tendency to remain in the same centile position from one age to another. For practical purposes it therefore usually suffices to have distance curves. Successive measurements will then show whether or not a child's head circumference growth conforms to the normal trend. A change upwards in the centile position or slowing down are indications for further examinations. Knowledge of the growth velocity of the head circumference is also of value in cases that raise a suspicion of pathological development or in which the effect of treatment is being followed episodically. We therefore present in this paper also the head circumference increments and their percentiles in a healthy child.

Material and Methods

The material of the present study comprises the Finnish Model Child series described in an earlier paper (2). The number of children measured appears from the appended tables, e.g. Table 1. Variations in the number of children are due to occasional non-attendance of some children or to omission of head circumference measurements on some occasions. If one measurement was missing it was interpolated in the same manner as in the case of body height and weight and sitting height (4). The proportion of interpolated measurements was as follows: boys, 12.7 per cent, girls, 12.3 per cent, both sexes, 12.5 per cent.

Results

In Table 1 are shown the mean head circumferences and their standard deviations at different ages. To facilitate practical application, distance curves drawn on their basis are given in Figs. 1a and 1b. The dispersion of the measurements is shown by curves of the means and standard deviations.

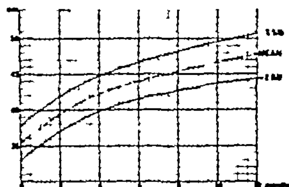
The head circumference increments are given in Tables 2a and 2b. The columns on the left show the mean measured growth and standard deviation in each stated age interval, and those on the right give the percentiles of annual growth velocity. The percentiles were sought in the same manner as those of height, weight and sitting height in a previous paper (4). The results are presented also as velocity curves, Figs. 2 and 3.

Discussion

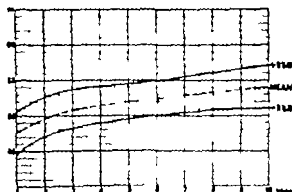
It is observed from the table on mean head circumferences that the head circumference of boys is slightly greater than that of girls throughout the growth period studied. This hypothesis is highly significantly true when statistically tested. During the first years of life the increase

Table 1. Mean head circumference of children aged from birth to 10 years (cm)

Age	Boys			Girls		
	Number of cases	Mean	SD	Number of cases	Mean	SD
0 months	44	35.4	1	57	34.6	1.
3	46	41.0	1	67	39.9	1.
6	48	44.0	1.3	67	43.2	1.3
9	47	46	1.4	60	45.1	1.5
1	5	47.4	1.5	71	46.5	1.3
15	48	48.6	0	61	47.1	1.4
18	46	49.0	1.4	61	47.8	1.4
1	38	49.6	1.7	58	48.4	1.4
4	47	49.8	1.5	66	48.8	1.4
.3 years	44	50.5	1.4	67	49.3	1.5
3.0	47	50.7	1.3	69	49.0	1.4
3.5	44	51.0	1.5	59	50	1.3
4.0	50	51.6	1.3	64	50.3	1.4
4.5	4	51.7	1.3	4	50.9	1.3
5.0	50	51.9	1.3	64	51.0	1.5
5.5	43	5 .0	1.3	57	51.3	1.5
6.0	50	5 .3	1.3	64	51.3	1.5
6.5	36	5 .6	1.3	45	51.7	1.3
7.0	44	52.8	1	55	51.8	1.4
7.5	33	53.0	1.4	44	0	1.4
8.0	37	53.4	1.2	47	52.3	1.4
8.5	28	53.7	1.3	38	5_.5	1.3
9.0	3	53.6	1.5	44	5 .7	1.5
9.5	26	53.5	1.7	31	5_.9	1.5
10.0	39	54	1.6	46	5 .9	1.3







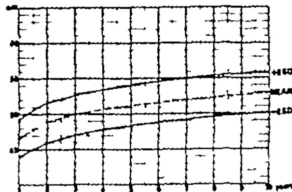


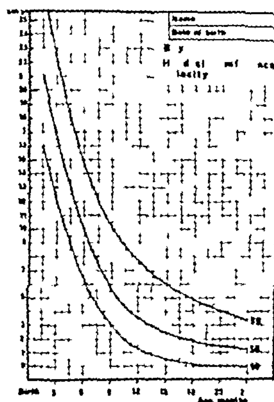
Fig. 1. Distance curves of head circumference for children aged from birth to ten years. (a) Boys. (b) Girls.

Table 2a. *Head circumference increments for boys aged from birth to 10 years*

Age interval	Measured growth, cm			Growth velocity cm/year		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	44	6.0	3.1	16.2	[illegible].2	[illegible]7.3
3–6 months	49	3.9	3.4	8.4	12.6	17.2
6–9	48	2.2	0.8	4.5	7.3	1[illegible].9
9–12	50	1.3	1.0	1.6	4.3	8.0
1[illegible]–15	51	1.1	1.4	1.1	3.3	7.0
15–18	47	0.7	0.6	0.3	2.[illegible]	5.7
18–21	43	0.6	0.7	0.0	1.8	3.8
[illegible]1–[illegible]4	44	0.6	0.6	0.0	1.7	4.8
[illegible]–[illegible]5 years	45	0.6	0.7	0.0	1.1	1.9
[illegible]5–3	46	0.4	0.4	0.0	0.6	1.5
3–3.5	48	0.4	0.3	0.0	0.8	1.6
3.5–4	47	0.4	0.5	0.0	0.6	1.9
4–4.5	43	0.4	0.8	0.0	0.2	1.6
4.5–5	43	0.3	0.3	0.0	0.5	1.5
5–5.5	40	0.3	0.2	0.0	0.2	1.1
5.5–6	45	0.3	0.3	0.0	0.5	1.2
6–6.5	40	0.3	0.2	0.0	0.2	1.2
6.5–7	38	0.3	0.4	0.0	0.2	[illegible].0
7–7.5	39	0.3	0.3	0.0	0.3	1.4
7.5–8	33	0.2	0.3	0.0	0.1	1.0
8–8.5	30	0.2	0.3	0.0	0.0	0.9
8.5–9	29	0.[illegible]	0.3	0.0	0.1	1.0
9–9.5	[illegible]3	0.3	0.4	0.0	0.2	1.5
9.5–10	26	0.3	0.4	0.0	0.1	1.6

Table 2b. *Head circumference increments for girls aged from birth to 10 years*

Age interval	Measured growth, cm			Growth velocity cm/year		
	Number of cases	Mean	SD	10th percentile	50th percentile	90th percentile
Birth-3 months	57	5.2	1.0	15.3	20.3	26.2
3–6 months	67	3.3	0.7	8.8	12.7	16.5
6–9	71	1.9	0.7	4.1	6.8	10.8
9–12	71	1.3	0.7	2.0	4.8	7.6
12–15	74	0.8	0.5	0.3	[illegible].8	5.6
15–18	63	0.7	0.5	0.0	2.4	4.8
18–[illegible]1	63	0.7	0.6	0.0	2.3	3.7
21–[illegible]4	6[illegible]	0.5	0.4	0.0	2.0	3.7
[illegible]–[illegible]5 years	63	0.5	0.5	0.0	0.8	2.1
2.5–3	64	0.6	0.5	0.0	1.0	[illegible]0
3–3.5	61	0.4	0.3	0.0	0.7	1.7
3.5–4	57	0.4	0.3	0.0	0.6	1.5
4–4.5	61	0.4	0.4	0.0	0.6	1.8
4.5–5	56	0.4	0.4	0.0	0.4	1.4
5–5.5	58	0.3	0.3	0.0	0.3	1.3
5.5–6	49	0.3	0.3	0.0	0.3	1.2
6–6.5	56	0.3	0.4	0.0	0.4	1.6
6.5–7	53	0.3	0.3	0.0	0[illegible]	1.3
7–7.5	49	0.3	0.3	0.0	0.[illegible]	1.3
7.5–8	45	0.3	0.4	0.0	0.3	1.7
8–8.5	41	0.3	0.3	0.0	0.3	1.3
8.5–9	39	0.4	0.4	0.0	0.3	1.2
9–9.5	39	0.[illegible]	0.4	0.0	0.0	1.2
9.5–10	36	0.3	0.6	0.0	0.1	1.5



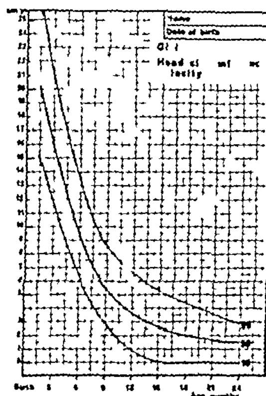
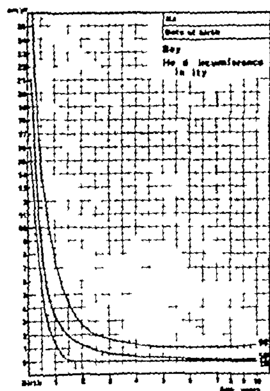


Fig. 2. Velocity curves of head circumference for children aged from birth to 24 months. (a) Boys. (b) Girls.



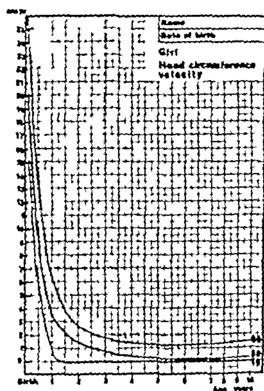


Fig. 3. Velocity curves of head circumference for children aged from birth to ten years. (a) Boys. (b) Girls.

Table 3. Mean head circumferences in English, Swedish and Finnish series, cm

Age	Boys			Girls		
	English children	Swedish children	Finnish children	English children	Swedish children	Finnish children
0 month	—	33.4	35.4	—	33.0	34.6
1	37.4	37.0	—	36.5	36	—
3 months	40.7	40.1	41.0	39.7	39.3	39.9
6	43.8	43.3	44.0	4[illegible].7	42.1	43.2
9	45.7	45.2	46.2	44.6	44.0	45.1
12	46.8	46.5	47.4	45.7	45.3	46.3
18	48.3	48.0	49.0	47.0	46.6	47.8
24	49.3	49.0	49.8	47.9	47.6	48.8
36	50.4	50.0	50.7	49.5	48.7	50.0

in the mean values is quite considerable 12 cm during the first year about 2.5 cm during the second year 0.9—1.2 cm during the third year and less than 1 cm thereafter For the sake of uniformity with our other studies, comparison of the results is made with measurements obtained in other series of children, i.e., a English series presented by Falkner (1) and a Swedish series of Karlberg *et al* (3). In Table 3 are given the mean values in these studies and in our present study at the ages for which corresponding data are available. The Swedish series shows consistently the lowest values and the Finnish series the highest values, the British values being between the two The differences between the extreme values are at the most 13 mm except in the newborn, among whom the mean values for boys show a difference of 20 mm.

The head circumference increments also establish that growth of this dimension is most active during the first years of life. The increments become quite small already in the third year After this the 50th percentile of growth velocity is only of the order of a few millimetres. Hence it is obvious that the 10th percentile value is zero In other words, during these years the head occasionally may not in all cases increase in size to a measurable degree. On the other hand it is also observed that the annual increment of the 90th percentile is of the magnitude of 1 0—1 5 cm per year The lower limits of increments, as we know are generally not of significance in these age groups, whereas the upper limits of increments are of clinical value

Karlberg *et al* (3) have also reported the increment means and standard deviations for time intervals that correspond to those of our study and a comparison of the results of these two studies is therefore possible, as is done

Table 4. Head circumference increments in Swedish and Finnish series, cm

Age	Boys		Girls	
	Swedish children	Finnish children	Swedish children	Finnish children
0—3 months	6.9	6.0	6.4	5.2
3—6	3.1	3.9	[illegible]	3.3
6—9	1.9	[illegible]	1.9	1.9
9—12	1.3	1.3	1.2	1.3
12—18	1.6	1.8	1.4	1.5
18—24	1.0	1.2	1.0	[illegible]
24—36	1.0	1.0	1.1	1.1

in Table 4 A similarity of the results is observed. The standard deviations are also of the same order of size. This comparison seems to indicate that the smaller series studied by us has given results that are as reliable as the somewhat larger series examined in Sweden in this respect.

Takkunen (5) has presented normal values for head circumference in a cross-sectional series of Finnish children. However the results now presented from a mixed longitudinal series cannot be compared with those of the larger cross-sectional series since all the children in the age range of for example 3 to 4 years were handled as one group by Takkunen. In a longitudinal series, as we know the mean value at any given age can be obtained from children of exactly the same age. Nevertheless, when the mean values obtained in these two series were entered on the same graph, the results were found to be in good agreement

Weight

Fig. 1 An example of -stage change upward and an 1 stage change down and in individual weight growth

relations. The birth height correlated highly significantly with the height at 3 months only its correlations with height at ages –5 years were almost significant (p 0 05) and those with later heights were not significant The height at 3 months correlated significantly with those measured at ages 3 7 years, but it did not have a significant correlation with the height at ages 8 9 or 10 The later measurements showed higher correlations with one another Only one non-significant correlation was seen in the period 1–10 years.

The correlations for weight (Tables 2a and 2b) give the same finding as those for height the correlations for boys were generally higher than those for girls. Nearly all of the boys correlations were highly significant. In the case of girls the birth weight did not appear to correlate significantly with the weight measured at 5 years and onwards. At all ages between 4 and 10 years, inclusive, the correlations were highly significant

II Centile position

Individual growth curves were drawn for each child on the normal height and weight growth curves. These curves were examined according to the above principles by the observers themselves.

Concerning the *height growth* we can observe that 41 per cent of the children in the present series did not change their position in the height centile at any time during the first 10 years of life At the age of 3 months, 50 per cent of the children were in the height centile in which they still were at the age of 10 years. Those who changed their position are examined more closely in Tables 3 4 and 5 A total of 5? per cent of the children advanced into a higher height centile Only 7 per cent descended into a lower height centile by one stage (> *1 SD) and none by two* stages (> ? SD) Each table shows the frequency in the series of those who changed position.

Table 1 *Correlation coefficients be ... he ght measurement of 37 bo ... from birth to 10 ... ar*

	Birth	3 mos	1 y	yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Birth	1 000											
3 month	[illegible]	1 000										
1	[illegible]	[illegible]	1 000									
[illegible]	[illegible]	[illegible]	0 840	1 000								
3	[illegible]		[illegible]	[illegible]	1 000							
4		[illegible]	[illegible]	[illegible]	0 933	1 000						
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0 943	1 000					
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0 850	0 908	1 000				
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	0 845	[illegible]	0 960	1 000			
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0 834	0 811	0 774	0 800	1 000		
[illegible]				[illegible]	[illegible]	[illegible]	[illegible]	0 671	0 688	0 835	1 000	
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0 774	0 757	0 737	0 873	1 000

4 ... 44 height ... part ... aof

Table 1b. *Correlation coefficients between height measurements of 76 girls from birth to 10 years*

	Birth	3 mos	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Birth	1.000											
3 months	0.588	1.000										
1 year	0.331	0.542	1.000									
2 years	0.270	0.413	0.778	1.000								
3	0.233	0.393	0.781	0.793	1.000							
4	0.260	0.406	0.711	0.683	0.833	1.000						
5	0.289	0.395	0.662	0.665	0.811	0.966	1.000					
6	0.184	0.336	0.595	0.684	0.680	0.805	0.828	1.000				
7	0.151	0.321	0.530	0.620	0.639	0.755	0.758	0.896	1.000			
8	0.115	0.225	0.379	0.452	0.498	0.646	0.679	0.792	0.850	1.000		
9	0.040	0.216	0.336	0.425	0.481	0.615	0.652	0.772	0.722	0.839	1.000	
10	0.143	0.135	0.228	0.320	0.353	0.488	0.547	0.662	0.701	0.836	0.727	1.000

.234 almost significant
.301 significant
.379 highly significant

Table 2a. *Correlation coefficients between weight measurements of 57 boys from birth to 10 years*

	Birth	3 mos	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Birth	1.000											
3 months	0.713	1.000										
1 year	0.622	0.676	1.000									
2 years	0.549	0.605	0.865	1.000								
3	0.599	0.597	0.777	0.829	1.000							
4	0.559	0.537	0.750	0.816	0.833	1.000						
5	0.535	0.498	0.650	0.697	0.774	0.913	1.000					
6	0.478	0.443	0.601	0.655	0.747	0.829	0.917	1.000				
7	0.467	0.468	0.601	0.625	0.765	0.803	0.878	0.916	1.000			
8	0.495	0.505	0.620	0.667	0.765	0.818	0.854	0.861	0.941	1.000		
9	0.406	0.418	0.570	0.651	0.715	0.751	0.744	0.751	0.868	0.914	1.000	
10	0.375	0.409	0.599	0.648	0.670	0.739	0.744	0.761	0.862	0.858	0.934	1.000

273 almost significant
354 significant
443 highly significant

Table 2b. *Correlation coefficients between weight measurements of 76 girls from birth to 10 years*

	Birth	3 mos	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs
Birth	1.000											
3 months	0.673	1.000										
1 year	0.418	0.648	1.000									
2 years	0.372	0.583	0.876	1.000								
3	0.385	0.552	0.704	0.744	1.000							
4	0.338	0.489	0.600	0.614	0.845	1.000						
5	0.255	0.401	0.504	0.526	0.817	0.939	1.000					
6	0.229	0.434	0.662	0.706	0.612	0.687	0.628	1.000				
7	0.228	0.404	0.579	0.687	0.546	0.636	0.577	0.920	1.000			
8	0.258	0.386	0.515	0.614	0.503	0.585	0.516	0.823	0.872	1.000		
9	0.145	0.348	0.485	0.579	0.471	0.565	0.500	0.762	0.806	0.868	1.000	
10	0.042	0.288	0.287	0.378	0.298	0.445	0.384	0.604	0.679	0.687	0.699	1.000

233 almost significant
301 significant
370 highly significant

Table 3. *Some facts on children who had advanced into a higher (≥ 2 SD) height centile*

FREQUENCY in the series ..5 per cent

POSITION AT BIRTH, mean 16th centile (range ..5th–50th centile)

POSITION AT 10 YEARS, mean 84th centile (50th–97.5th centile)

First change of centile position

Birth-3 mos	46 per cent	91 per cent
3–6	1	
6–12	15	
1–2 yrs	9	
Later	9	

Mean duration 8 6 mos (3–36 mos)

Second change of centile position

Before 2 yrs	43 per cent
2–7	4
7–10	33

Mean duration 34 8 mos (3–114 mos)

Table 4. *Some facts on children who had advanced into a higher (≥ 1 SD) height centile*

FREQUENCY in the series 77 per cent

POSITION AT BIRTH, mean 16th centile (range 5th–84th centile)

POSITION AT 10 YEARS, mean 50th centile (16th–97.5th centile)

CHANGE OF CENTILE POSITION

Birth-3 mos	.. per cent	70 per cent
3–6	14	
6–1	17	
1–2 yrs	13	
5	11	
5–7	14	
7–10	6	

Mean duration ..5 0 mos (3–90 mos)

Table 5. *Some facts on children who had descended into a lower (≥ 1 SD) height centile*

FREQUENCY in the series 7 per cent

POSITION AT BIRTH, mean 50th centile (range 50th–84th centile)

POSITION AT 10 YEARS, mean 16th centile (5th–50th centile)

CHANGE OF CENTILE POSITION

Birth	[illegible]	8 per cent
3	[illegible]	
6–1	[illegible]	
1–2 y	[illegible]	
2–7	[illegible]	

Mean duration 1 4 [illegible]

their position at birth and [illegible] attained at age 10. They also [illegible] the changes of position occurr[illegible] mean duration of the change of po[illegible]

Those children who within 10 years advanced to two stages higher positions (Table 3) had undergone the first change during, on the average, 8 months in 91 per cent of these it had occurred before the age of 2 years. The mean duration of the second change of position was as long as nearly 3 years and it occurred at an even rate between the ages of and 10 years. For those children who advanced by only one stage the time required for this change of position was longer being mean 25 months. Also in this instance the majority changed the position during the first two years of life. However in 30 per cent of the children it occurred after age 2.

Table 5 shows the behaviour of the 9 children (7 per cent of the series) whose height growth descended from the original position by one standard deviation. At birth all of these children had been in the 50th centile position or higher. The change of position required on the average slightly less than two years and in the majority of cases occurred before the age of 2 years.

The mean height of the fathers of those children who advanced two stages was 177 8 cm, which is 2.1 cm taller than the mean height of all fathers in this series. The mothers also were 1 6 cm taller on the average than the mean of all the mothers. These differences have no statistical significance because of the smallness of the group, but they may give an indication of a greater hereditary growth potential of these children than of other children in the present series. This group includes 6 children who had advanced in height by as much as three standard deviations. The parents of these 6 children were definitely above the average in height. None of the children who changed position upwards were found to have endocrine disorders. They have now been followed up to puberty and nothing unusual has been observed in their state of health.

On examining the illness history of the children of retarded height we found that only one of them had a faultless state of health at the time of descent in centile position. The group included 4 children with frequent respiratory infections at that time. Two other children had

T ble 6. *Some facts on children ho had caught up after descent in height position*

Name	Sex	Centile position at birth	Age interval in which centile position descended	Diseases at that time	Age at hich centile position regained	Centile position at 10 years
L.H.	*Girl*	*16th*	*Birth-3 months*	*Vomiting, suspected cerebral lesion*	*5 months*	*50th since age 5*
A.F.	Girl	50th	Birth-3 months	Malnutrition	1 year	84th since age 2
T.K.	Girl	50th	Birth-3 months	Vomiting	6 months	84th since age 2
J.P.	Girl	16th	Birth-3 months	Diarrhoea + respiratory infections	5 months	50th since 6 months, 84th at 10 yrs
T.K.	Girl	16th	Birth-6 months	Insufficient feeding	16 months	50th since age 3
P.J.	Girl	50th	Birth-18 months	Frequent respiratory infections	2.5 years	84th at 7—8 years, 97.5th thereafter

had frequent respiratory infections and vomiting. One had suffered from difficulties in feeding. One child had a congenital dislocation of the hip for which she was six months on an abduction pillow splint. It is very hard to say what role these illnesses had on the children's height growth. None of these children caught up in growth, as would have been expected if the illnesses had had a transient effect. All of these 9 children remained in their new centile position. Our series included, in addition, 6 girls (described in Table 6) who descended temporarily in the height position and later clearly caught up in growth. At the age of 10 all of them were in a higher centile than at birth. During the change in position they had had respiratory infections, vomiting, and in two cases malnutrition because of depletion of the breast-milk.

In the *weight* of the children in our series there occurred numerous transient one-stage changes both up and down, for instance in 58 per cent during the first two years of life. A summary table of these children was therefore not prepared. Those who ascended or descended two centile positions are summarized in Tables 7 and 8. Twenty-six per cent of the series advanced

Table 7. *Some facts on children ho had advanced into higher (≧ 2 SD) eight centile position*

FREQUENCY in the series   26 per cent

POSITION AT BIRTH, mean 16th centile (range 2.5th—97.5th centile)

POSITION AT 10 YEARS, mean 84th centile (16th—97.5th centile)

First change of centile position

Birth-3 mos	34 per cent	83 per cent (Birth–2 yrs)
3—6	23	
6—12	20	
1—2 yrs	6	
Later	17	

Mean duration 12.8 mos (3—60 mos)

Second change of centile position

Before 2 yrs	34 per cent
— 7	34
7—10	32

Mean duration 28.0 mos (3—84 mos)

Table 8. *Some facts on children ho had descended into lower (≧ 2 SD) eight entile position*

FREQUENCY in the series   7.5 per cent

POSITION AT BIRTH, mean 84th centile (range 84th—97.5th centile)

POSITION AT 10 YEARS, mean 16th centile (16th—50th centile)

First change of centile position.

Before 3 mos	80 per cent
3—6	20

Mean duration 3.2 mos (1.5—6 mos)

Second change of centile position

Before 3 mos	30 per cent
3—12	20
1— yrs	10
2— 7	40

Mean duration 21.2 mos (1.5—72 mos)

[illegible] SD) in height [illegible]

[illegible] in the series [illegible] per cent

[illegible] BIRTH [illegible] centile (range [illegible])

[illegible] YEARS mean [illegible] centile ([illegible] 97 [illegible])

[illegible]
46 per cent
[illegible]
15
9
9
([illegible] 36 mos)

[illegible]
43 per cent
4
33
3 [illegible] (14 mos)

[illegible] who had advanced one stage higher [illegible] SD [illegible] height [illegible]

[illegible] per cent

[illegible] BIRTH [illegible] centile ([illegible] 50th)

[illegible] YEARS [illegible] 50th centile (16th–97.5th)

CHANGE OF CENTILE POSITION
[illegible] per cent
[illegible] 14
[illegible]
[illegible] 0 per cent
11
14
10 6

Mean duration 50 mos (3–90 mos)

Table 5. Some [illegible] who had descended [illegible] lower [illegible] SD [illegible] height [illegible]

FREQUENCY in the series 7 per cent

POSITION AT BIRTH mean 50th centile (range 50th–84th centile)

POSITION AT 10 YEARS mean 16th centile (5th–50th centile)

CHANGE OF CENTILE POSITION

Birth-3 mos	— per cent	
3–6	11	78 per cent
6–1[illegible]	22	
1[illegible]	33	
[illegible]	[illegible]	

Mean duration 1[illegible] mos (3–72 mos)

their position at birth and the position attained at age 10. They also show the ages at which the changes of position occurred, and the mean duration of the change of position.

Those children who within 10 years advanced to two stages higher positions (Table 3) had undergone the first change during, on the average, [illegible] 8 months; in 91 per cent of these it had occurred before the age of 2 years. The mean duration of the second change of position was as long as nearly 3 years and it occurred at an even rate between the ages of 2 and 10 years. For those children who advanced by only one stage the time required for this change of position was longer, being mean 25 months. Also in this instance the majority changed the position during the first two years of life. However, in 50 per cent of the children it occurred after age 2.

Table 5 shows the behaviour of the 9 children (7 per cent of the series) whose height growth descended from the original position by one standard deviation. At birth all of these children had been in the 50th centile position or higher. The change of position required on the average slightly less than two years and in the majority of cases occurred before the age of 2 years.

The mean height of the fathers of those children who advanced two stages was 177.8 cm, which is 2.1 cm taller than the mean height of all fathers in this series. The mothers also were 1.6 cm taller on the average than the mean of all the mothers. These differences have no statistical significance because of the smallness of the group, but they may give an indication of a greater hereditary growth potential of these children than of other children in the present series. This group includes 6 children who had advanced in height by as much as three standard deviations. The parents of these 6 children were definitely above the average in height. None of the children who changed position upwards were found to have endocrine disorders. They have now been followed up to puberty and nothing unusual has been observed in their state of health.

On examining the illness history of the children of retarded height w[illegible] found that only one of them had a faultless state of health at the time of descent in centile position. The group included 4 children with frequent respiratory infections at that time. Two other children had

Discussion

I Correlations between successive measurements

The literature contains a number of longitudinal growth studies in which the correlation has been established measurements taken in early childhood and those taken later in life. Tanner *et al* (8) has presented in his paper based on the Aberdeen growth study the correlation coefficients between the body measurements at 0, 1 2, 3 4 and 5 years and the adult measurements of the same individuals. The measurements from 1 year onwards were found to correlate with all later measurements with correlation coefficients over 0 65. The same author (9) has also reported pooled data from the international collaborative longitudinal study It was observed that the measurements at 8 years were very poorly predicted from measurements in the first 3 months after birth, but by the age of 1 year the correlations had risen, especially for head circumference and supine length ($r \geq 0\ 7$)

The fact that similar results were obtained in our present study can be considered to indicate that this series, although small in size, behaves similarly and is therefore suitable for establishment of the standards for Finnish children. We also observed that the correlation, especially for boys, between height at 1 year and at later ages up to 10 years was higher than 0 65 The correlations between birth and 3 months were lower but in boys nearly all of these correlations, too were highly significant, whereas for girls the correlation coefficients appeared to be lower than those of boys. Weight measurements appeared to behave in the same manner even if the correlation coefficients for both boys and girls were somewhat lower With respect to both height and weight it was observed that particularly the measurements at birth correlated poorly with the later values. This finding, as well as the results obtained also in studies elsewhere speak for the opinion that the size of the newborn is mostly determined by the prenatal environment during the last two months of pregnancy Uterine nutritional circumstances and the mother s physique probably have importance in this (6), but not yet the genetic growth potential

II Centile position

There is an unknown mechanism that controls the organism s homeorhesis, or tendency to remain in and return to its path of growth. It is interesting to study on the base of a longitudinal series how well individuals follow their own centile positions. Garn (3), for example, studied how the individual growth of girls in Boston conformed to the channelwise grid progression of Wetzel (11). The girls who had remained in their initial channels up to the age of 1 year made up 50 per cent of the series, by the age of 2 their number had dropped to 19 per cent, and also later the proportion of those who remained in the initial position was low under 33 per cent. The criteria used by us for a change of centile position differ from those applied by Garn, but in any case definite deviations from the original "channels" become evident in the same way in both studies. The proportion of children who remained in their own centile for height throughout the first 10 years of life was 41 per cent of our total series. During the first 2 years 4? per cent had remained in their original centile for weight.

The general observation was made that upward changes were very numerous and that these occurred during varying lengths of time. This result was to be expected since, as we have already shown in another study (10), the mean values in this series of children shift already at pre-school age significantly above the curves used for comparison. As we have discussed earlier this can be ascribed to two causes Firstly the curves used in the comparison were based on a series of children born on the average 10 years earlier than the children in the present series, and secondly our series is comprised entirely of urban children. The influence of the secular trend and of possible environmental factors becomes more clearly evident after infancy

Roughly a half of the children in the present

series changed their centile position. A detailed examination revealed two types of changes in centile position. During infancy there was a rapid shift upwards or downwards, and after infancy the change was generally upwards and took place during a longer period, two or three years. A fall in the height centile was rare in our series and occurred mostly in infancy and at a slow rate. Tall mothers' babies with a high birth weight form the majority of the group that underwent a rapid downward change in weight position. These children's own genetic growth potential points to possible paternal inheritance. More probably however the loss of weight was associated with adaptation. On the other hand, again, the children of tall parents are found in the group which later had a tendency to move into higher centiles. It is a well known fact that weight growth is more readily disturbed by external factors than height growth is, though these two growth parameters frequently are linked together (5). In our series, one of every two children who descended two stages in weight underwent a change of the same direction also in height.

With some rare exceptions, the children in this series had undergone no severe illnesses. Coincidently with centile changes there were more than the average number of mild illnesses. An unexpected finding was that catch-up growth which Garn (3) and Prader *et al.* (5) consider to be almost the rule, was noted in only about a third of the children who had changed height percentile. With one exception the downward change in centile position had occurred in these by the age of 6 months and all of them were at the age of 10 years in a centile position that was above that at birth. The cases in which catch up growth did not occur showed no essential difference from the preceding group with respect to illness history. It is open to question whether the mild illnesses in our series played any definite part in the changes of percentile. Would it possibly have been merely a question of the child seeking its own channel of growth during the first months of life irrespective of any illnesses?

On examining the predictability of a child's height at 2 years from its height at birth it was found that an accurate prediction would have been possible for 65 per cent of the children. The height at 10 years would have been predictable in 60 per cent at already the age of 2. The quite numerous one stage deviations from the growth centiles at the age of 10 are equivalent to a difference of as much as 5 cm in height and 5 kg in weight from the expected values. Since no descents whatsoever in the centile position for height occur in actual life after infancy, it can be said that by means of the distance curves it is possible to predict at least the shortest height a child will reach within the next few years. The predictability with respect to weight is slightly poorer but quite good.

Summary

Using the measurements of a longitudinal growth study the correlations between successive height and weight measurements of 133 children from birth to the age of 10 were calculated and the centile positions of each child on cross-sectional distance curves were examined during this period. The ages concerned were birth, 3 months, 1 year and full years up to age 10.

The correlations between the successive height measurements were in general high and statistically significant. Boys had higher correlation coefficients than girls. The height at birth correlated more poorly with the later measurements than the annual measurements in the interval from 1 to 10 years. In the 1—10 year period the correlations were $r > 0.7$ for boys and > 0.3 for girls, and they were all statistically significant. Also the correlation coefficients for boys were in nearly all cases highly significant and higher than those for girls. The birth weights of girls did not correlate significantly with the weights at 5 years and onwards, but at all ages in the period 4—10 years the correlations were highly significant.

The children who remained throughout in the same centile position in the cross-sectional curves for height made up 41 per cent of the series. A change upwards in the centile position by $\geq$ 1 SD occurred in ?7 per cent of the children and by $\geq$ 2 SD in 25 per cent, and a change downwards by $\geq$ 1 SD occurred in 7 per cent. None of the children moved 2 SD downwards in the height centile. In weight a change upwards by $\geq$ 2 SD occurred in 26 per cent and downwards by $\geq$ 2 SD in 7.5 per cent. Changes of less than 2 SD were not analysed. From these it was observed that the child changes its centile position either during the first year of life, when the change occurs during a short period or in later years, when the change requires about two years.

In the intervals 0—2 years and ?—10 years about 60 per cent of the children remained in their own centile positions with respect to height and weight. Those who changed position appeared to have a definite tendency upwards. Changes downwards were clearly less frequent. During the first two years of life there were more descents in the centile position and during the following eight years there were more ascents.

In seeking the etiological causes of the centile changes it was observed that the parents of the children who clearly advanced rapidly in height were taller than the mean for the whole series. Children of mothers who were above the mean in weight were numerous in the group that moved downwards in centile position. In the other groups the size of the parents did not differ from the mean for the series.

The morbidity of the children who descended in centile position of both height and weight growth was studied. About 80 per cent were found to have had a transitory illness at the time of change of centile position. Six of the 15 children who were retarded in height showed clear catch up growth after recovery from the illness, but the others continued in their new lower centile position even after recovery. Neither was definite catch up growth seen during the observed period in the children who were clearly behind in weight. No chronically ill children were included in the present series.

References

1. Bäckström-Järvinen, L. Heights and eights of Finnish children and young adults. *Ann Paed F nn 10* Suppl. 23 1964
2. Bäckström, L. & Kantero R. L. C oss-sectional studies of height and eight in Finnish children ged from birth t 20 years. *Acta Paediat Scand*, Suppl. 220 9, 1971
3. Garn, S. Individual and group deviations from channelwise grid progression in girls. *Child Dev lop 23* 193 1952
4. Hallman, N. Bäckström-Järvinen, L., Kantero, R. L. & T mala, R. Finnish Centre for Study in Child Growth and Development. *Ann Paediat Fenn 1* 8, 1966.
5. Prader A., Tanner J M & von Harnack, G. A.: Catch-up growth following illness or starvation. An example of developmental canalization in man. *J Pediat* 62 646, 1963.
6. Rhabl, C. E. Gestational age, size and maturity. Pregnancy toxaemia and maternal cardio- ascular efficiency. *Clinics in Developmental M dicine* No. 19 50 1965.
7. T kkunen, R. L. Anthropometric studies on Finnish children. *Ann Paediat Fenn 8* Suppl. *19* 1962
8. Tanner J M. Healy M., Lockhardt, R., MacKenzie, J & Whitehouse, R. Aberdeen growth study I The prediction of adult body measurements from measurements taken each year from birth to 5 years. *Arch Dis Childh 31* 372, 1956.
9. Tanner J M Goldstein, H., Graffar M Ascel, M Karlberg, P Prader A. & Sempé, R.: Predictability of children' measurements up to 8 years from their n and their parents measurement: An international collaborative longitudinal study (Abst) *XII Int n Congr Pediat* 461 1968
10. Tihula, R & Kantero, R.-L. Comparison of height nd weight distance curves based on longitudinal and rosssectional series from birth to 10 year *Acta Paediat Scand* Suppl 220 13, 1971
11. Wetzel, N. Physical fitness in terms of physique, development and basal metabolism. *JAMA 116* 1187 1941

Key ords Height growth, eight growth, catch-up growth, correlations between successive mea urements

Table [illegible] Par[illegible]-child [illegible]relation [illegible]eff[illegible]ient for height f[illegible]om birth to 10 [illegible] of age

	Birth	3 month	1 year	[illegible] yrs	3	4	5	6	7	8	9	10
Son-Mother	0.344	0.47	0.518	0.494	0.487	0.454	0.431	0.330	0.328	0.460	0.413	0 [illegible]66
Son-Father	0.296	0.357	0.317	0.371	0.447	0.425	0.364	0.366	0.350	0.451	0.308	0.197
Son-Midparent	0.348	0.447	0.446	0.464	0.507	0.474	0.426	0.379	0.364	0.504	0.385	0 [illegible]49
Daughter Mother	0.211	0.393	0.374	0.338	0.376	0.453	0.414	0.370	0.[illegible]36	0.195	0.[illegible]61	0.164
Daughter Father	0.205	0 [illegible]47	0.354	0.3[illegible]4**	0.390	0.410	0.451	0.336	0.288**	0.303	0.379	0.3[illegible]1
Daughter Midparent	0 [illegible]43	0.381	0.4[illegible]7	0.391	0.4[illegible]	0.501	0.505	0.382	0.306	0.293	0.358	0.[illegible]61
Child Midparent	0.791**	0.395	0.419	0.417	0.456	0.48	0.467	0.382	0.335	0.409	0.377	0 [illegible]68

p [illegible] 0.05 *p* [illegible] 0.01 *p* [illegible] 0.001

T[illegible]ble 3 *Parent-child [illegible]orr[illegible]lation [illegible]efficient for [illegible]ight from birth to 10 y[illegible]ar[illegible] of age*

	Birth	3 months	1 year	[illegible] yrs	3	4	5	6	7	8	9	10
Son-Mother	0.4[illegible]**	0.358	0.380	0.414	0.39	0.437	0.508	0.482	0.446	0.451	0.401	0.380
Son-Father	0.330	0.337	0 [illegible]4	0.265	0.326	0 [illegible]47	0.294	0.[illegible]19	0.188	0.179	0.069	0.035
Son-Midparent	0.454	0.426	0.375	0.428	0.436	0.414	0.483	0.415	0.370	0.365	0.280	0.[illegible]30
Daughter Mother	0.364	0.327	0.390	0.[illegible]98	0.371	0.372	0.349	0.301	0.[illegible]65	0.289	0.283	0.109
Daughter Father	0.193	0.197	0.155	0.206	0.226	0 [illegible]44	0.[illegible]30	0.138	0.175	0.208	0.266	0.162
Daughter Midparent	0.340	0.319	0.330	0.305	0.366	0.374	0.349	0.[illegible]60	0.[illegible]59	0.[illegible]91	0.3[illegible]4	0.159
Child-Midparent	0.378	0.323	0.312	0.339	0.383	0.376	0.390	0.3[illegible]1	0.299	0.323	0.30[illegible]	0.177

p [illegible] 0.05 *p* < 0.01 *p* [illegible] 0.001

Table 4. *Correlation coefficients between height of child and skeletal age*

	Chronological age, years					
	1	3	5	7	9	10
Boys	0 211	0.32	0 4.4	0.469	0.393	0.408
Girls	0.295	0 296	0.408	0 526	0 540**	0.563**

$p < 0.05$
** $p < 0.01$
** $p < 0.001$

Table 5. *Correlation coefficients between skeletal age of child and height of parent*

	Chronological ages, years					
	1	3	5	7	9	10
Son-Mother	0 293	0 124	0.163	0.101	0.167	0.332
Son-Father	0.142	0 098	0.126	0.144	0 080	0.178
Son-Midparent	—	—	—	0.133	0 128	0.264
Daughter Mother	0..46	0.046	0.290	0.361**	0.095	−0.025
Daughter Father	−0 018	0.117	0.152	0.188	−0 0.1	−0.047
Daughter Midparent	—	—	—	0.300	0.041	−0 038

$p < 0.05$
$p < 0.01$

correlation coefficients were higher from the age of 5 onwards than at ages 1 and 3.

Child's skeletal age and parents heights These correlation coefficients are presented in Table 5 The correlations were on the whole positive, but the only statistical significance seen was the almost significant ($p < 0.05$) correlation to mother s height at some ages. The only significant one ($p < 0.01$) was the daughter-mother correlation at age 7 The correlations with the father s height even were negative for girls at some ages, and also for boys they generally were lower than the correlations with the mother s height. However when statistically tested the parent progeny differences between the sexes were not significant.

Discussion

Our series is fairly homogenous with respect to the external factors that influence growth. This refers to its socio-economic composition (8) as well as to morbidity (3). It would thus seem that genetic factors have in this series a central position in governing of the individual variance in growth.

In height and weight the parents in this series are representative of the normal Finnish population (2) Furthermore the height and weight of the two parents showed a statistically significant positive correlation and therefore there apparently was, on the whole, no heterosis in the genetic background of the children in this series.

The clearly positive parent-child correlation for *height* in our series is in agreement with the observation in other longitudinal studies (4 5 7 9 12, 15 17) In the present series the correlation for height attained definite statistical significance at already the age of 3 months, and the correlation coefficients increased further up to the age of 5 years. The best material for comparison is the international collaborative longitudinal study up to 8 years (15), in which the correlations were low during the first 6 months of life but rose rapidly thereafter to approach the figure 0.4 by age 2 and the adult value of 0.5 by age 8.

The like-sexed and unlike-sexed correlations in our series were roughly equal and no statistically significant differences were demonstrable between them. Highly conflicting observations have been reported in the literature on the

17 Tanner J M & Israelsohn, W J Parent-child correlations for body measurements of children between the ages one month and seven years. *Ann Hum Genet* 26 245 1963.

18 Tanner J M Whitehouse R H & Healy M J R. A new system for estimating skeletal maturity from the hand and wrist, with standards derived from a study of 2600 healthy British children II The scoring system International Children Centre, Paris 1962.

19 Tiisala, R., Kantero, R. L., Backstrom, L. & Hallman, N A mixed longitudinal study on skeletal maturation in healthy Finnish children aged 1 to 5 years. *Hum Biol*, 41 360, 1969

20. Yudkin, J Psychological and social aspects of dietary habits. *In Nutrition in Preschool and School Age* Symposia of the Swedish Nutrition Foundation 1969 VII p. 99

A ord Heredity in growth

(R. L. K.) Children's Hospital,
University of Helsinki
Stenbackstreet 11
Helsinki 29
Finland

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge)

161. Friesen, T. and Hermann, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr 20.— 1965
162. Landmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr 30.— 1965
164. Bergner, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 28.— 1966
165. Gleason, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis. A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 25.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr 35.— 1966
167. Jensen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr 30.— 1966
168. Trojaborg, W. Focal Spike Discharges in Children. Longitudinal Study. Sw. kr 25.— 1966
169. Dahl, Mogens, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr 30.— 1966
170. Bellman, Margot, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 25.— 1966
172. *Festschrift in Memory of Constantin Chernois.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Pettersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hänninen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 28.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress, Bergen, 1967.* Sw. kr. 35.— 1967
178. Sjögren, Ishan, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using a Passive Haemagglutination Technique. Sw. kr 28.— 1968

Koch, Gösta, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 28.— 1968

Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968

Robertson, Alan F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr 25.— 1968

Petersson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968

Andersen, Else, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968

Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968

Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1968

Meeuwisse, Gerard W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and a Genetic Study. Sw. kr 25.— 1969

Fillström, S. P. On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr 20.— 1969

Hårnbäd, P. Tagre, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 28.— 1969

Karvälä, Antti, Cardiovascular Responses of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr 30.— 1969

Vahere, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 38.— 1969

Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969

194. Kumento, Antti, Studies on the Serum Binding of Vitamin B12 in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thoren, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 30.— 1969
197. Fosnäs, Kerva, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 28.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Snyder, Dora M., Cravioto, Joaquín, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette E., Hartroft, Phyllis, Balis, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kristian, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Kvarnström, Ernst and Fröhlen, Osbrun, The Insensible Water Loss of the Newborn Infant. Sw. kr 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Mauri Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 35.— 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. Sw. kr 35.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Hakulinen, Aino, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr 35.— 1971
214. Samuelson, Göran, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr 25.— 1971
215. Bergsman, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr. 25.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium, Stockholm, August 30–September 1, 1970.* Edited by Claes Thorén. Sw. kr. 35.— 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 35.— 1971
219. Jaffé, Doris, Hartroft, Stanley, Manning, Mary and Eleta, Graciela, Coronary Arteries in Newborn Children, Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. Sw. kr. 25.— 1971
220. Hallman, Niilo, Bäckström, Leena, Kantero, Raija-Liisa and Tiisala, Ritva, Studies on Growth of Finnish Children from Birth to Ten Years. Sw. kr. 38.— 1971

Price Swed. kr 30 —

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

transverse section from each of the three main coronary arteries from 12 male and 12 female newborn infants. He measured the area of *intima and media in each section and found* the male intima to measure 6 of the media, while the female intima measured only 8 He stressed this sex difference and expressed the belief that the familial inciden e of coronary disease is to a significant degree related to the inherited characteristics of the coronary in tima

The following year Fangman & Hellwig (9) reported their findings derived from 15 male and 15 female neonates Apparently Dock had not examined his preparations for lipid but Fangman & Hellwig did and proposed a new theory as a result. While agreeing with Dock *that there was a significant sex difference* (on the basis of finding cushion like" intimal thicken ngs in 8 of 15 males and 4 of 15 females—most often in the left anterior de scending branch) they considered the lipid to be of primary importance They described fine deposits of lipid along elastic fibres and in the *stroma of cushions, and sometimes also in large* histiocytes. This finding persuaded them that the primary event in the formation of cushions was the precipitation of lipoid and they were therefore unable to accept Dock s interpreta tion that the cushions were inherited anatomic peculiarities"

The same year 1947 Minkowski (27) published data from his series of coronary arteries from 704 infants, including a group of 76 neonates Intimal bolsters were noted in 43 of the 51 newborn males, and in 35 of the 75 females No lipid studies were mentioned Minkowski was not convinced that the sex difference was really significant in his series and he felt that the meaning of the *thi k ning particularly in relation to the* subsequ nt development of coronary athero-scl r osis, emained to be clarified

Fi e years later came Moon & Rinehart s observations on the histogenesis of coronary arteriosclerosis (28) derived from a series of 50 cases of all ages They found that the earliest seen lesion was characterized by the apparently simultaneous appearance of proliferation of subendothelial fibroblasts, increased *amounts of mucoid ground substance and fragmentation* of the internal elastic membrane" A pr mary ground substance alteration was suggested—that is, a hyaline" degeneration resulting from abnormal polymerization of ground substance No relationship between these earliest changes and the occasional pres*ence of fine droplets of lipids could be demon* strated.

Lober (25), in 1953 provided a detailed report on a series of 536 cases, ranging in age from newborn to the ninth decade and in cluding a group of 25 less than one month old—15 male and 10 female In this group, *the average thickness of intima as a percentage* of the thickness of the artery wall was found to be for the male infants, 15 and for the female 12 —not a mathematically significant difference No histological information on these early thickenings is provided in this report.

A paper by Schornagel (39) *in 1956* dealt again with early histological changes. He chose to examine 2 cm segments from the left anterior descending coronary arteries of 88 infants ranging in age from newborn to one year He graded the intimal changes, 1 2 or 3 Grade 1 required endothelium lying directly on IEL of regular structure or only a splitting of the lamina grade 3 required a thick intima, not necessarily circular Changes of grades 2 and 3 were found in 8 of 20 (40%) of the male infants up to 1 day old, and in 5 of 21 (23 8%) of the female. This sex difference was not regarded as significant According to Schornagel, the primary changes as a rule consist in splitting of the lamina elastica in*terna, followed by the formation of the* intima with the stellate cells of Langhans, i.e., cells of a mesenchymal nature, the *formation of* elastic fibers, and ingrowth of muscle fibers" Lipid was detected in some cases" Schornagel found a considerable increase in intimal thick ening during the first year of life, in agree

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 219 197

CORONARY ARTERIES IN NEWBORN CHILDREN

INTIMAL VARIATIONS IN LONGITUDINAL SECTIONS AND THEIR RELATIONSHIPS TO CLINICAL AND EXPERIMENTAL DATA

BY DORIS JAFFÉ, W STANLEY HARTROFT
MARY MANNING AND GRACIELA ELETA

ALMQVIST & WIKSELL PERIODICAL COMPANY

ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 219 1971

From The Research Institute The Hospital for Sick Children, Toronto, Canada

CORONARY ARTERIES IN NEWBORN CHILDREN

Intimal variations in longitudinal sections and their relationships to clinical and experimental data

by

Doris Jaffé W Stanley Hartroft
Mary Manning and Graciela Eleta

UPPSALA 1971

This investigation was supported by
the Ontario Heart Foundation, by the Medical
Research Council of Canada and by Intramural
funds supplied by The Hospital
for Sick Children, Toronto

Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
UPPSALA 1971

During recent years, the paediatric aspects of coronary heart disease have become increasingly a subject for discussion. Developments in several areas of research have all contributed to this awakening interest. Firstly examination of coronary arteries from American soldiers killed in Korea revealed that severe stenosing atherosclerosis was disturbingly common among these young and apparently healthy men (7) Secondly the rising mortality from ischaemic heart disease is affecting especially the younger age groups (57) Thirdly preventive measures begun in later life, although worth while in some instances, are proving to be quite inadequate for the present situation (4 49). And fourthly familial hyperlipoproteinaemia type II, which is associated with an extremely high risk of premature heart disease, and which is a fairly common condition, may now be diagnosed in early infancy (14) and treated in childhood (23)

Today therefore, the question of excessive atherosclerosis in early life must concern every one involved in child care, and the feasibility of preventing some of the potentially harmful changes in the arteries of children and young people must now be considered.

But what are these early changes? How soon do they occur? And under what circumstances? To help answer these questions, we need to look closely at the changes occurring in arteries from successive age groups then, we should seek an explanation for developments that appear excessive or abnormal, through study of clinical and experimental data. In this report, we shall review earlier papers describing and evaluating histological findings in the coronary arteries of newborn children we shall add some observations derived from our own series, and we shall examine interrelationships of histological findings and clinical data, in the light of recent experimental work. We hope in this way to provide a set of base-line findings that will be of help in the evaluation of changes found in older age groups.

REVIEW OF LITERATURE

An awareness of early intimal changes in human coronary arteries has existed for many years, following reports describing progressive intimal growth beginning in infancy and continuing throughout life. We may find a useful review of this earlier European literature in an article by Ehrich et al. (1931) (6) who added their own description of the growing layers of intimal tissue observed in a series of 51 hearts, 5 of which were from newborn infants. They noted, again, the early developments of the elastic–muscular (musculo–elastic) layer then the inconstant elastic–hyperplastic layer and finally the third and innermost, the hyperplastic (connective tissue) layer with its proneness to undergo atherosclerotic changes. The first detectable alteration in this sequence of events was apparently "a splitting up at several points of the lamina elastica interna" found in all newborn cases near the origin of the left anterior descending branch.

In 1934 Cross et al. (15) examined 50 hearts from the first 8 decades and again reported, as the primary changes, a splitting of the internal elastic lamina (IEL) and formation of the musculo-elastic layer (MEL) and secondary internal elastic lamina. These alterations were seen by the third month—again, in the left anterior descending branch

In 1946 came the first of a number of papers in which the arteries of newborn children were singled out for special attention. Dock (5) probably stimulated this interest by introducing a new idea. He had examined a

transverse section from each of the three main coronary arteries from 12 male and 12 female newborn infants. He measured the area of intima and media in each section and found the male intima to measure .6" of the media while the female intima measured only 8 . He stressed this sex difference and expressed the belief that the familial inciden e of coronary disease is, to a significant degree related to the inherited characteristics of the coronary in tima

The following year Fangman & Hellwig (9) reported their findings derived from 15 male and 15 female neonates. Apparently Dock had not examined his preparations for lipid but Fangman & Hellwig did, and proposed a new theory as a result. While agreeing with Dock that there was a significant sex difference (on the basis of finding cushion-like" intimal thicken ngs in 8 of 15 males and 4 of 15 females—most often in the left anterior de scending branch) they considered the lipid to be of primary importance. They described fine deposits of lipid along elastic fibres and in the stroma of cushions, and sometimes also in large histiocytes. This finding persuaded them that the primary event in the formation of cushions was the precipitation of lipoid" and they were therefore unable to accept Dock s interpreta tion that the cushions were inherited anatomic peculiarities

The same year 1947 Minkowski (27) published data from his series of coronary arteries from 704 infants, including a group of 76 neonates. Intimal bolsters were noted in 43% of the 51 newborn males, and in 35 of the 25 females No lipid studies were mentioned. Minkowski was not convinced that the sex difference was really significant in his series, and he felt that the meaning of the thickenings, particularly in relation to the subsequent development of coronary atherosclerosis, remained to be clarified

Five years later came Moon & Rinehart s observations on the histogenesis of coronary arteriosclerosis (28) derived from a series of 250 cases of all ages They found that the earliest seen lesion was characterized by the apparently simultaneous appearance of proliferation of subendothelial fibroblasts, increased amounts of mucoid ground substance and fragmentation of the internal elastic membrane" A primary ground substance alteration was suggested—that is, a hyaline" degeneration resulting from abnormal polymerization of ground substance No relationship between these earliest changes and the occasional presence of fine droplets of lipids could be demonstrated.

Lober (25) in 1953 provided a detailed report on a series of 536 cases, ranging in age from newborn to the ninth decade and including a group of 25 less than one month old—15 male and 10 female In this group the average thickness of intima as a percentage of the thickness of the artery wall was found to be for the male infants, 15 and for the female 12" —not a mathematically significant difference No histological information on these early thickenings is provided in this report.

A paper by Schornagel (39) in 1956, dealt again with early histological changes. He chose to examine 2 cm segments from the left anterior descending coronary arteries of 88 infants ranging in age from newborn to one year He graded the intimal changes, 1 2 or 3 Grade 1 required endothelium lying directly on IEL of regular structure or only a splitting of the lamina, grade 3 required a thick intima, not necessarily circular Changes of grades 2 and 3 were found in 8 of 20 (40%) of the male infants up to 1 day old, and in 5 of 21 (23 8%) of the female. This sex difference was not regarded as significant. According to Schornagel, the primary changes as a rule consist in splitting of the lamina elastica interna, followed by the formation of the intima with the stellate cells of Langhans, i.e. cells of a mesenchymal nature the formation of elastic fibers, and ingrowth of muscle fibers" Lipid was detected in some cases" Schornagel found a considerable increase in intimal thickening during the first year of life, in agree-

ment with earlier investigators who described progressive age-changes. He expressed the belief that the infantile intimal thickening should be interpreted as a normal physiological phenomenon of adaptation But, he concluded, I am convinced, on the other hand, that this intimal thickening provides a basis for the coronary sclerosis regularly encountered in old age" He pointed out the similarity of the intimal thickening in his sections to "the so-called intimal cushions, described by Zinck, Hirsch & Bucher as occurring especially at bifurcations" nevertheless, he believed that observers should take care not to confuse them.

In 1956 also Levene (24) reported studies on 98 cases of various ages, including premature and stillborn infants. In 1 of 5 premature infants, he noted focal lesions of the internal elastic lamina"—that is, a localized splitting with no overlying thickening Of 15 full term infants 9 had these lesions" and some had, in *addition*, an overlying early fibrous thickening" Levene believed that the early elastic lesions" were the basis for the development of the classical atheromatous lesions. Finally he introduced a topic that had not been discussed before in reports on the very early thickenings. He had found superficial fibrinous encrustations in 7 of his cases, including two stillborn infants, and he concluded that, undoubtedly *the deposition and incorporation of* fibrin from the blood is responsible for at least some of the progressive intimal thickenings No lipid studies were undertaken by Levene.

Moon s second contribution to this literature came in 1957 (29) with his observations on the coronary arteries of 105 foetuses, infants and juveniles, ranging in age from 0 to 22 years. He noted "no lesions of the internal elastic lamina or intima" in the 24 foetuses, but described rupture and fragmentation of the internal elastic lamina in newborn infants, associated with deposition of acid mucopolysaccharides, fibroblastic proliferation and occasionally endothelial proliferation" Lipid was not mentioned in these youngest cases. Regarding the nature of the thickenings, Moon expressed the belief—presumably derived from this entire series—that the thickenings are identical with the early non-lipid phases of arteriosclerosis in adults. He mentioned finding sex differences at all ages, the male exhibiting the greater degree of intimal thickening.

All studies outlined so far involved infants in areas of Western civilization" where the incidence of coronary heart disease is high. To see if there might be some relationship between the early thickenings and a proneness to later heart disease, Robertson (36) now examined the intima of newborn infants in a part of the world where coronary heart disease was uncommon In 1960, he reported findings derived from 30 African (Nigerian) neonates —19 male and 11 female. In sections from the left anterior descending artery and from the circumflex, he found cushion-like thickenings in the wall, consisting of reduplications" of the internal elastica and bundles of longitudinal muscle. These thickenings were found in 16 of the 30 cases—in 11 of the 19 male infants, and in 5 of the 11 female. Lipids were not investigated. Robertson already familiar with the arteries of European newborns, considered that the African vessels were histologically the same as their European counterparts. He concluded that the condition of the intimal cushions in the vessels of the newborn plays little part in determining the later development of arteriosclerosis.

In a separate report, Robertson (37), also in 1960, discussed "stress zones" in foetal arteries. These vessels were mostly peripheral, but he did include coronary arteries from 8 cases in his series. In 4 of these he found intimal cushions similar to thickenings observed in the peripheral arteries. In one of these cases, lipid was found, both in the coronary and in the peripheral cushions. Robertson noted that, characteristically the thickenings in both coronary and peripheral arteries were found in the mouths of branches and in those vessels subject to pulsation. He considered them to be physiological in nature—a response of the vascular wall to the stresses produced by focal

areas of impaired pulsation—and not degenerative. Arterial cushions apparently originated in foetal life. Their most important constituent was found to be bundles of longitudinal muscle. Both intimal thickening and splitting of the internal elastica were believed to be brought about by a radial reorientation and migration of the muscle cells of the media. Evidently Robertson did not share the view expressed by Schornagel in 1956, that bifurcation cushions and other thickenings were to be regarded as separate entities.

Gillot (13) in 1962, compared the coronary arteries of 46 white and 69 Bantu children up to 12 years of age. No differences were noted between the races, nor between the sexes. Unlike Robertson, Gillot believed the thickenings were pathological.

The same year Neufeld et al. (31) studied coronary developments from intra-uterine life to 39 years of age, in a series of 100 cases, including 10 foetuses. Three specimens were taken from each case—from the right, from the left near the origin, and from the beginning of the left anterior descending branch. Lipid was not studied. In 3 of the 10 foetuses, localized splitting of the IEL was found, with "smooth muscle fibres longitudinally between the internal elastic lamina and intima". In some areas "proliferation and thickening of the intimal layer" was observed. As to whether or not the MEL and foci of intimal fibrous thickening should be regarded as normal, the authors were uncertain. They believed, however, that the higher development of both types of thickening in the male than in the female, at any given age, supplied circumstantial evidence that these changes might underlie the process of atherogenesis.

Because, in Israel, the incidence of myocardial infarction was known to be lower in immigrants from Yemen than in Ashkenazy Jews, Vlodaver et al. (51) investigated the coronary arteries of 50 Yemenite foetuses and infants up to 1 year old. Three sections were taken from each of the 30 male and 20 female infants—from the left and right coronary arteries 0.5 cm from their ostia, and from the anterior descending branch of the left coronary 0.5 cm below its commencement. Changes observed, and reported in 1967, were characterized by "localized and diffuse splitting of the internal elastic membrane with proliferation of subendothelial fibroblasts and deposition of mucopolysaccharides; the gradual development of the musculo-elastic layer first in the intima and then in the media, and mild fibrosis of the outer layer of the media." These developments were considered similar to the changes described by other investigators in non-Yemenite infants—North American, European and African. The similarity of all these infant groups, despite the differences in incidence of coronary heart disease in the adult populations, suggested to the authors the earliest intimal changes are not of great importance in the subsequent development of atherosclerosis in adult life. They were in complete agreement with Robertson and Gillot on this point. They speculated that the "lesions" in the coronary arteries of foetuses and infants were likely to be of a physiological nature, due to changes in the haemodynamic conditions which resulted in the appearance of the MEL. In this Yemenite series, the two sexes had about the same amount of intima at birth, and the male showed no tendency to acquire a thicker intima than the female, during the first year of life. The authors wondered if this similarity of intimal bulk in both sexes might have a bearing on the low incidence of atherosclerosis in the adult Yemenite males.

In a separate study, Vlodaver & Neufeld (52), also in 1967, focussed upon the relationship of MEL development to post-natal haemodynamic events in a series of 80 foetuses and infants—35 female and 45 male. Again transverse sections were taken from the right and left coronary arteries and from the left anterior descending branch. Lipid was not investigated. The authors described a sequence of events occurring within the first 12 months of life: the first phase (termed "reactive") in-

volved degeneration of muscle cells and elastic laminae along with proliferative changes the second phase (adaptive") was characterized by the development of the musculo-elastic layer as a response to haemodynamic changes following birth. Thus, formation of MEL was regarded as a stage in the vasogenesis of the coronary arteries in man. No mention was made of MEL in newborn infants, but it was noted that the reactive phase" might already be under way before birth. This phase was de scribed as follows, The internal elastic lamina loses its folds and undergoes splitting, and the adjacent smooth muscle cells of the media lose their shape and position and show degenerative changes. With the occurrence of these changes, a proliferation of fibroblasts and an increase of mucopolysaccharide appear under the endothelium."

And now in 1969 came a study by Vlodaver et al. (53) suggesting that although different populations may have similar vessels at the time of birth, an ethnic group susceptible to coronary heart disease may soon thereafter develop a much thicker intima than the others. The series examined consisted of coronary arteries from 211 full term foetuses, infants and children up to 10 years of age, of Ashkenazy Yemenite and Bedouin origin. Statistical analysis showed the musculo-elastic layers to be more developed in the Ashkenazy males than in the Yemenite and Bedouin males. These differences are apparent soon after birth, but are more obvious at the end of the first year of life." Also, Ashkenazy males clearly have more intima and musculo-elastic tissue than do the Ashkenazy females"

In all studies outlined above, intimal thickenings have been observed—usually in slightly less than half of the cases in each series. (Here, one needs to be aware of differences in terminology for some authors, "intima" extends all the way between the endothelium and internal elastic lamina, but, for others, it is a narrower zone that excludes the musculo-elastic layering.) Precisely where these cushions are located within the arteries has not been made clear although a predilection for the left anterior descending branch is strongly suggested. The internal elastic lamina beneath the cushions has been described as split up" fragmented and reduplicated and focal elastica disturbances, without overlying thickening, have sometimes been observed. Opinions have varied regarding the type of cells that predominate within the cushions in recent years, most authors have regarded them as smooth muscle cells, but a subendothelial fibroblastic proliferation" is described by some investigators.

An important question not yet satisfactorily resolved is whether or not the thickenings are more prominent in male than in female infants.

Whether the earliest lipid deposits do or do not cause intimal thickening remains an open question requiring further study Despite Fangman & Hellwig's lipoid theory of origin of atherosclerosis, later investigators apart from Robertson apparently have seldom looked for lipid in their specimens from newborn infants.

Evidence so far suggests that intimal thickening in different newborn groups is identical, regardless of whether they are derived from populations that suffer much or little coronary heart disease later in life. Of special interest is the recent study (53) suggesting that, soon after birth, an ethnic group susceptible to coronary heart disease may develop a much thicker intima than non-susceptible groups.

Opinions have varied widely regarding the significance of the newborn thickenings—in particular their relationship to atherosclerosis. This apparent lack of agreement may be attributable to different interpretations of the terms atherosclerosis" and arteriosclerosis" which persistently interfere with clear communication in this field, despite the WHO definition of atherosclerosis we now have (56)

None of the reports reviewed have included a study of the interrelationships, in individual cases, of clinical history and arterial changes an approach of this kind seems useful, if a reason is to be found for any excessive or abnormal intimal alterations.

2 – 718?

MATERIALS AND METHODS

1 *Examination of arteries*

We studied the coronary arteries from 176 infants (109 male and 67 female) dying in the first month (31 days) of life.

Hearts were fixed in cobalt formalin. The extramyocardial portions of the coronary arteries were dissected free intact. Labelled sketches of gross specimens were made to aid in relating microscopic features to the branch pattern of each artery

Originally one of each pair of arteries was paraffin-embedded and the other was frozen for sectioning. Later all were gelatin-embedded (54) to permit study of lipid in every vessel.

Arteries from all but 3 infants were cut at close intervals longitudinally the 6 vessels f om the exceptions were serially sectioned trans ersely as an aid to envisioning a composite artery in 3 dimensions.

Paraffin sections were stained routinely with haematoxylin and eosin, phosphotungstic acid haematoxylin, orcein, periodic acid Schiff Alcian blue Prussian blue and von Kossa stains. Frozen sections were stained with oil red O (ORO) haematoxylin and light green, ORO haematoxylin and aldehyde fuchsin, ORO haematoxylin and orcein, van Gieson and aldehyde fuchsin, and Masson s trichrome.

Preparations containing lipid in appreciable quantity as shown in ORO-stained sections, were further examined for interceroids and ceroid (16).

Several specimens were examined for cholesterol, by Schultz s method (26).

Sections were examined by light microscope. Findings were recorded for each case in drawings which showed the extent, depth and structure of every intimal thickening found, and the location and form of ll isible lipid W regarded as intima all tissue on luminal aspect of the internal elastic lamina) An intimal thickening for the purposes of is study was defined as an area in which both cells and fibres were interposed between IEL and endothelium. Extent of intimal thickening seen in each artery was graded as follows. 0 (none seen), + (minimal one or two small areas only), + + or + (intermediate) or (widespread—most of le ible surface)

2. *Investigation of elationships of linical dat to histol gical finding and of interrelationships of histological findings*

Clinical data and histological findings were recorded for each case on forms designed for use in study of all age groups.

Clinical data noted er primary diagnosis (50), secondary diagnosis, sex eek of gestation, ge weight, heart eight (onl t dying ithin first 4 day of life only), height maternal disease family history and feeding (breast-feed g bottle-feeding, or both)

Histological findings el ted er presence of unusually bulky intimal thick g or unusually abundant intimal lipid, or both (nl sections considered adequate for this assessment extent of intimal thickening, depth of intimal thickening, presence and type of IEL alterations, presence of intimal lipid (extracted and unextracted (16), intracellular and extracellular (droplets or debris or both)), cholesterol, excessive cellular infiltration, encrustation, focal increase of f brosis, intramural haemorrhage, intimal vascularization, and undue medial disturbance.

Using these data, we undertook the following studies in 157 of our cases (sections from 19 cases, although providing useful information, were not regarded as adequate for these studies):

1 An analysis of the way in which diagnosis, sex, gestation period, age, weights of body and heart, and feeding were related to extent and volume of intimal thickening, to amount of intimal lipid, to intimal oedema, and to cellular infiltration.

2. A search for possible associations among intimal changes considered excessive for this age group.

RESULTS

1 *Examination of arteries*

Fig. 1 summarizes our findings, in diagrams of the proximal portion of a representative artery Media in major coronary vessels varied from about 3 cells thick, in early premature to about 8 in full term infants. Medial defects were present at branch sites, as shown in the uppermost diagram. In most areas, intimal thickening was absent—that is, endothelium lay directly on smooth intact IEL. But in almost all specimens intimal thickenings were found, accentuated as shown at branch sites where they formed smoothly rounded pads. In some cases, intimal development was slight compared to that illustrated in the diagrams, while in others it was more extensive or more massive. All gradations in between were encountered, without any sharp cut-off" point between thick and thin.

Approximately one quarter of our specimens were assigned to each of the grades of extent (+ + + + + + or + + + +).

The thickest intima usually lay as noted, at points of branching, and in the main trunks where it was usually asymmetrical. In most vessels with adequate sections, one or more areas of intimal thickening that equalled or exceeded the underlying media in depth were found extending beyond branch pads. Intimal thickening was often more extensive and

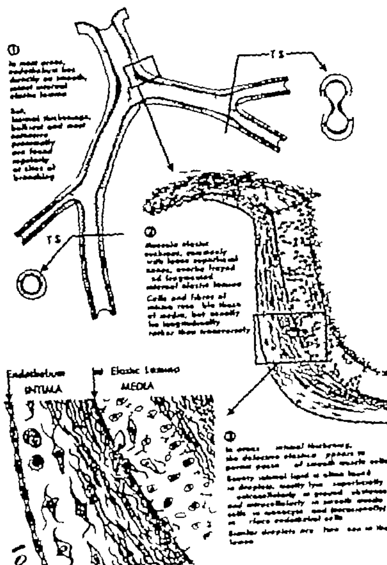


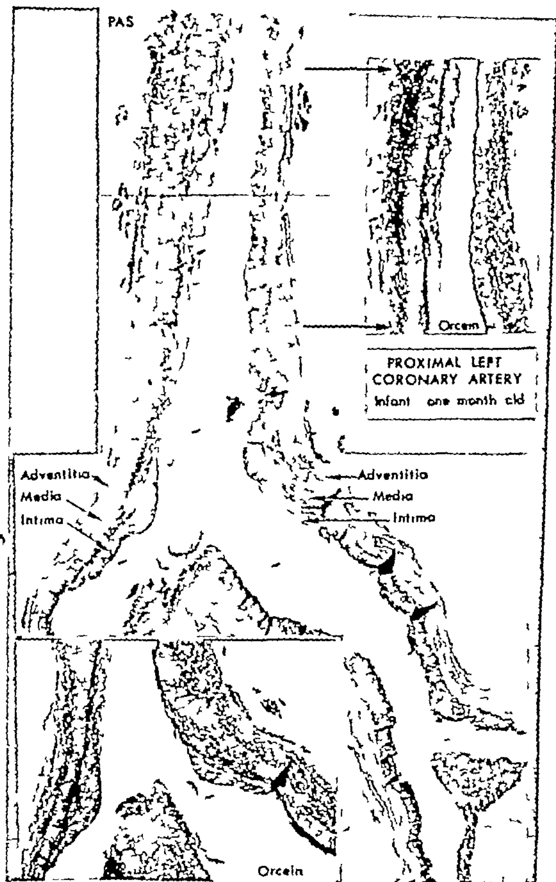
Fig. 1 Composite diagrams of newborn coronary artery. In diagram 1, intimal thickenings are shown in black; altered internal elastic lamina is represented by dotted lines underlying thickenings.

deeper in the left coronary artery than in the right; we did not encounter the reverse situation in any infant. Intimal thickening was regarded as unusually bulky for this age group in 35 of the 157 cases with sections thought adequate for this assessment. In Fig. 2, showing intimal thickening in the proximal portion of one vessel, intimal tissue is somewhat bulkier than usual for the newborn age group; oedema is also present.

As shown in the diagrams (Fig. 1), intimal thickenings consisted largely of musculo-elastic layering (MEL) in which cells and fibres resembled those of the underlying media but were usually orientated longitudinally rather than transversely.

In continuity with branch pads, zones of less conspicuous MEL extended for varying distances along the vessel walls (Figs. 1 and 2). Underlying all thickenings, and extending for varying distances beyond them, were areas of altered IEL. Not all MEL and areas of elastica changes were necessarily in continuity with branch pads; separate patches could be found, in serial transverse sections.

In the areas of altered IEL referred to above, the normally smooth and refractile lamina was usually dull and longitudinally frayed, and


PAS
Orcein
PROXIMAL LEFT
CORONARY ARTERY
Infant one month old
Adventitia
Media
Intima
Adventitia
Media
Intima
Orcein

often thinned and fragmented. Frequently fine wavy tendrils, often in large numbers, arose from the upper surface, rippling along the lamina in the slightly widened subendothelial space (Figs. 3 and 4). Beneath gaps in fragmented areas of IEL, muscle cells usually lay out of alignment in their locally disturbed and weakened fibrous scaffolding. Frequently muscle cells were found, singly and in groups, between separated remnants of IEL, neither "medial" nor yet "intimal" but intermediate in position.

In Figs. 5 and 6, smooth muscle cells appear on the luminal aspect of IEL, lying longitudinally as was usual for muscle cells on this side of the lamina. MEL has thus developed. Figs. 7 and 8 also illustrate MEL—of moderate degree in Fig. 7 and relatively thick in Fig. 8. An unusually bulky and oedematous intima is shown in Fig. 9

Unlike most of the thickenings elsewhere, intimal tissue in branch pads had a tendency to form two zones—a compact deeper one similar to MEL that did not underlie pads, and a loose superficial one with abundant ground substance stellate cells and relatively few fibres (Fig. 10) In some vessels, the loose superficial zone continued beyond branch cushions. Usually no clear line of demarcation was present between the two zones, where the compact and the loose tissue merged, we found many cells with features intermediate between those of the superficial stellate cells and the underlying elongated muscle cells of the compact zone. Intimal ground substance stained positively with Alcian blue, denoting the presence of acid mucopolysaccharide (AMP). AMP appeared to be especially plentiful at branch sites, because of the abundance of ground substance in branch cushions.

Within intimal thickenings, fibres often became aligned to form secondary ("reduplicated") laminae ranging in appearance from ill-defined cobwebby structures to substantial fenestrated sheets resembling fully developed IEL. In the presence of a well formed secondary lamina, the basal IEL was usually widely defective, as shown in Fig. 6 In such areas, the line of demarcation between intima and media was often uncertain. Intimal fibres, whether separate or aligned to form laminae, stained completely with orcein. But, in sections stained with PTAH, certain fibres remained colourless or were only partly stained. Colourless fibres predominated in the developing IEL of premature infants, and among the fine wavy tendrils in intimal thickenings. Delicate cores of PTAH-positive material were visible within some of these fibres. With increasing maturity IEL acquired more of this PTAH-positive substance until, at term, only a residual sheath of unstained material coated the lamina. In areas of IEL alteration, the fine curling intimal tendrils appeared to arise from the ensheathing substance and not from the PTAH-positive elastica core. In the stages of acquiring PTAH positive cores, the more substantial intimal fibres apparently behaved like developing IEL among the secondary laminae formed by intimal fibres, we recognized all stages of development observed in the maturation of normal IEL.

Oedema. In 27 of 157 cases, some or all of the intimal tissue was regarded as excessively loose with undue amounts of intercellular fluid (oedema) either separating muscle bundles, as in Fig. 9 or raising the endothelium, as in Fig. 11 or both.

Lipid Stainable lipid was visible in 55 of the 134 cases with adequate ORO-stained sections filed. We found lipid in 21 of the 29 cases in which both arteries had been completely gelatin-embedded, that is, when a superior technique was adopted for demonstrating intimal lipid, it was found in more than 2 out of 3 cases.

In 46 of the 55 cases with ORO-positive sections, lipid was scanty—sometimes visible in

---

Fig. 2 Proximal portion of left coronary artery. Longitudinal section showing intimal thickenings, with typical pads at bifurcations. Intimal tissue proximal to main bifurcation is bulky and oedematous. (Case no. 147 in Table 1 One month, male, crib death. Paraffin-embedded, PAS and orcein.)



Fig. 3. Minimal alterations of internal elastic lamina. Longitudinal section showing delicate wavy fibres in *slightly widened subendothelial space (centre right).* (Two days, male premature respiratory distress syndrome intracranial haemorrhage. Paraffin-embedded, orcein.)



Fig. 4. Slightly more advanced alterations of elastica. Longitudinal section showing conspicuous wavy fibres running longitudinally in widened subendothelial space. (Two days, male, premature, respiratory distress syndrome, intracranial haemorrhage. Paraffin-embedded, orcein.)



Fig. 5. Typical slight musculo-elastic layering. Longitudinal section showing wavy intimal fibres and defective basal elastic lamina. Smooth muscle cells (arrows) lie in a gap in the lamina and longitudinally in the intima. (Case no. 135 in Table 1 Stillborn, female 43 weeks gestation. Paraffin-embedded orcein.)



Fig. 6. Typical musculo-elastic layering. Longitudinal section showing widely defective basal elastic lamina (left). Distinction between intima and media disappears in this area. (Case no. 135 in Table 1 Stillborn, female, 43 weeks gestation. Paraffin-embedded, orcein.)

only a few pale droplets in an occasional cell, or a light focal sprinkling of extracellular droplets, or as a faint pink tinge of the ground substance. In the remaining 9 ORO-positive cases, lipid was regarded as unusually abundant for the newborn age group

Concentration of lipid varied considerably within the intima of a single specimen a predilection for loose cushion tissue was generally noticeable. Intensity of ground substance staining and concentration of extracellular ORO-positive droplets were usually greatest immediately beneath the endothelium, and gradually decreased towards the deeper intima. No lipid was found external to IEL in any case, and no staining of the elastica itself was observed.

Some lipid-free sections contained massive intimal thickenings, and, conversely other specimens with comparatively large amounts of lipid had only a thin layer of intima to contain it.

In many cases, ORO-positive droplets were found intracellularly as well as, or instead of extracellularly Cells containing lipid varied in appearance: some were smooth muscle cells, a few monocytes, and some were unidentified. Many of the affected cells contained only a few small droplets, but others were filled with relatively large globules. In one specimen scattered lipid-laden cells had ruptured, releasing lipid debris in a bulky bifurcation cushion (Fig. 12).

Sometimes we found ORO-positive staining of the blood serum or plasma in the lumen. In some cases, but not in others, it closely matched the lipid-staining of the adjacent intimal ground substance. Occasionally we found intracellular ORO-positive droplets in bloodstream round cells, in the lumen.

Interceroid and ceroid Interceroid but no ceroid was detectable in two of 14 specimens examined for these substances.

Cholesterol Schultz's test for cholesterol, performed on 4 specimens with more than the usual amounts of lipid, was positive in 2.

Cellular infiltration. Scattered subendothelial cells with the appearance of lymphocytes or monocytes were found in almost all specimens, they were usually most readily found in the subendothelium of larger branch cushions. In most vessels, infiltrations were scanty they were considered unusually heavy in 7 cases. Subendothelial cells of bloodstream type are visible in Figs. 7 10 and 11

Encrustation. In one case only we recognized a surface encrustation—a microscopic thrombus fused to a branch cushion. The only infiltration of polymorphonuclear cells found in this newborn series was present in this area of encrustation.

Necrosis We noted small amounts of necrotic material in only one specimen (already referred to under Lipid"), in a bulky bifurcation cushion that contained scattered disintegrating lipid-laden cells (Fig. 12).

Fibrosis. Focal increase in intimal fibrosis was recognized in one case with scattered hary deposits of a substance with staining qualities



Fig. 7 Moderate musculo-elastic thickening. Longitudinal section with fibres barely visible, but cells of media and intima clearly seen lying in typical transverse and longitudinal directions. As is usual, MEL is asymmetrical. A subendothelial round cell is present (left). (Case no. 135 in Table 1. Stillborn, female, 43 weeks' gestation. Paraffin-embedded, H & E.)

and appearance suggestive of altered fibrin or collagen. Part of this unusual vessel is shown in Fig. 11

Haemorrhage and vascularization Neither was seen, in this series.

Medial disturbances. Disturbances in excess of the usual disarray underlying intimal thickenings involved parts of several specimens. These appeared to have no special relationship to changes in the overlying intima.

2. *Relationships of clinical data to histological findings and interrelationships of histological findings*

In Table 1, cases are classified according to diagnosis. Data on sex, maturity survival time



Fig. 3. Minimal alterations of internal elastic lamina. Longitudinal section showing delicate wavy fibres in slightly widened subendothelial space (centre right). (Two days, male premature, respiratory distress syndrome intracranial haemorrhage. Paraffin-embedded, orcein.)



Fig. 4. Slightly more advanced alterations of elastica. Longitudinal section showing conspicuous wavy fibres running longitudinally in widened subendothelial space. (Two days, male, premature respiratory distress syndrome, intracranial haemorrhage. Paraffin-embedded, orcein.)

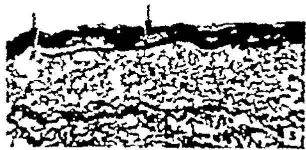


Fig. 5. Typical slight musculo-elastic layering. Longitudinal section showing wavy intimal fibres and defective basal elastic lamina. Smooth muscle cells (arrows) lie in a gap in the lamina and longitudinally in the intima. (Case no. 135 in Table 1. Stillborn, female 43 weeks gestation. Paraffin-embedded orcein.)



Fig. 6. Typical musculo-elastic layering. Longitudinal section showing widely defective basal elastic lamina (left). Distinction between intima and media disappears in this area. (Case no. 135 in Table 1. Stillborn, female, 43 weeks gestation. Paraffin-embedded, orcein.)

only a few pale droplets in an occasional cell, or a light focal sprinkling of extracellular droplets, or as a faint pink tinge of the ground substance. In the remaining 9 ORO-positive cases, lipid was regarded as unusually abundant for the newborn age group.

Concentration of lipid varied considerably within the intima of a single specimen: a predilection for loose cushion tissue was generally noticeable. Intensity of ground substance staining and concentration of extracellular ORO-positive droplets were usually greatest immediately beneath the endothelium and gradually decreased towards the deeper intima. No lipid was found external to IEL in any case and no staining of the elastica itself was observed.

Some lipid free sections contained massive intimal thickenings, and, conversely other specimens with comparatively large amounts of lipid had only a thin layer of intima to contain it.

and weights are included along with histological findings thought to be most relevant. Tables 2 to 6 are derived from data contained in Table 1

Relationship of diagnosis and histological findings. Wide variations in the state of the intima are evident within most of the diagnostic categories. None of the histological findings listed in Table 1 appears especially prevalent in any of the larger categories. Most diagnostic categories contain too few cases to show whether or not the disease that caused death was related to any of the histological features. But two of these categories attract attention. In 3 of the 5 cases of "Congenital Anomalies of the Circulatory System" an excessively thick intima was found. And both of the babies in the "Sudden Death" category (cases of crib death) had a bulky oedematous intima.

In the intima of the only two infants known to have received exchange transfusions (cases 60 and 61), excessive lipid was present. The excess was due largely to extracellular infiltrations of myriads of ORO-positive droplets that were more conspicuous in these infants than in any others in the newborn series.

Maternal diabetes, noted in 3 cases (numbers 6, 93 and 114), was not associated with unusual findings in two of the infants, one of whom died of hyaline membrane disease (HMD) and the other of meningitis. The third baby who died of HMD did have intimal thickening regarded as excessive.

Intimal thickenings were absent from the sections in 6 cases, including both cases of hydrops foetalis (cases 65 and 70) and the case with glucose-6-phosphate dehydrogenase deficiency (case 34—a Chinese infant)

Relationship of sex and histological findings. Table 2 provides a comparison of histological findings in male and in female infants. None of the findings listed were found to differ significantly in the two sexes.

Relationship of age and histological findings Table 3 discloses no definite relationship between days of survival and histological findings, nor between period of gestation and histological findings.

Relationship of weights (of body and of heart) and histological findings. In infants who died during the first 4 days of life (81 cases altogether) neither body weight (Table 4) nor heart weight (Table 5) was found related in any definite way to the state of the intima. We note, however that 8 of the 10 instances of intimal oedema occurred among the 40 infants with the heavier body weights, and among the 40 infants with the heavier hearts.

Relationship of feeding and histological findings Because only two infants (cases 146 and 147) were likely to have received normal feedings, no attempt was made in this age group to explore the relationship of arterial changes to diet.

Interrelationships of histological findings. These are shown in Table 6. We see that, in the great majority of cases with bulky intima, lipid was not noted to be excessive—that is, lipid was either scanty or absent, or its amount was unknown. On the other hand, in the majority of arteries with bulky intima, oedema was present.

Fig 8 Thick musculo-elastic layering. Longitudinal section showing typically asymmetrical thickening with only slight changes in opposite wall of artery (Case no 80 in Table 1 13 hours, male, full term, hyaline membrane disease Paraffin-embedded, orcein.)

Fig 9 Bulky intimal thickening. Longitudinal section showing marked oedema separating muscle bundles. Media, distinct on the left, runs across bottom of photograph and disappears into chaotic musculo-elastic tissue on right. (Case no. 19 in Table 1 Seven hours, male full term, diaphragmatic hernia. Paraffin-embedded, orcein.)

DISCUSSION

In our series, we found longitudinal sectioning of intact branching specimens of great value in disclosing intimal thickenings that would not have been seen in the more usual transverse sections taken at some distance from the major sites of branching. The technique of embedding intact vessels has the added ad-

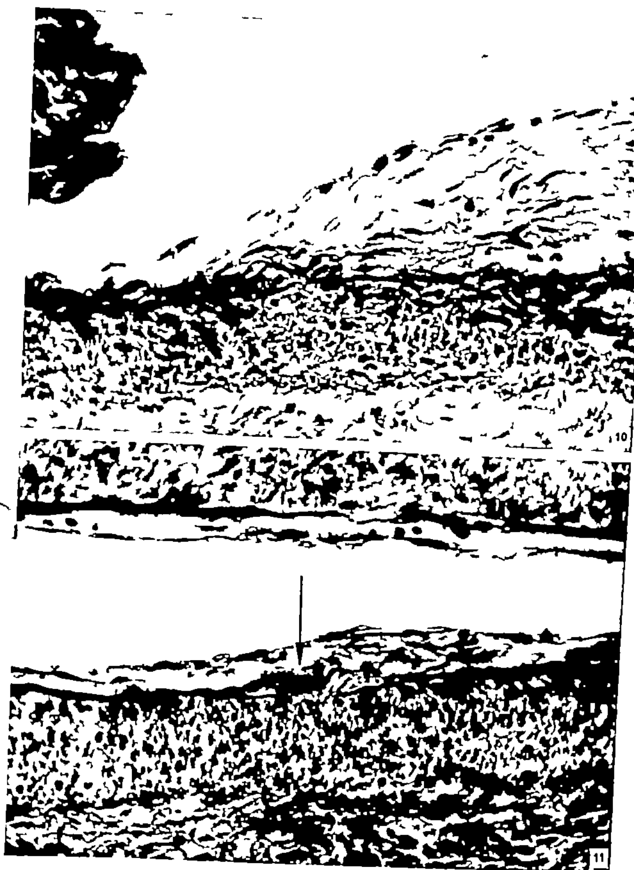

10
11



Fig. 12. Branch cushion with lipid. Longitudinal section showing relatively abundant lipid, both extracellular (dark haze in lumen and superficial intima) and intracellular (large dark cells lying in intimal "clearings") (arrows). A few lipid-laden cells are disintegrating. Wall structure is characteristically disturbed beneath cushion, which appears swollen with oedema fluid. (Case no. 146 in Table 1. Three weeks, male, crib death. Gelatin-embedded, ORO light green and haematoxylin.)

vantage of preserving much of the luminal contents, usually lost in processing by other methods, and almost certainly lost if perfusion techniques are used.

Fig. 10. Part of branch pad. Longitudinal section showing characteristic loose superficial zone, more compact deep layer and defective basal elastic lamina with loss of distinction between intima and media. Transition from cushion tissue to compact MEL on left. (Case no. 14 in Table 1. 48 hours, male, premature intrauterine pneumonia, septicaemia. Paraffin-embedded, PTAH.)

Fig. 11. Abnormal intima. Longitudinal section showing oedema fluid and round cells in widened subendothelial space and focal wall disturbances at IEL defects. At one IEL gap, we note apparent proliferation of smooth muscle cells and unusual accumulation of material staining as collagen or altered fibrin (arrow). (Case no. 27 in Table 1. 17 days, male, full term, hydranencephaly, bronchopneumonia. Paraffin-embedded, PTAH.)

Our sections clearly showed that intimal cushions at branch sites were often continuous with MEL extending along the vessel walls. All thickenings, at branch sites and elsewhere, appeared basically alike, although they varied widely in their detailed pattern of cells and fibres, and in the quantity of ground substance present. We are unable, then, to share the view that bifurcation cushions and other thickenings are separate entities (39).

Cushioning found in bifurcation areas appeared similar in distribution and structure to the thickenings described by Stehbens in cerebral arteries of human infants (43), sheep and steers (45), and in the renal arteries of rabbits (44). The unvarying location of pads in certain positions at bifurcations suggested to Stehbens that haemodynamic factors had been operative in their formation, and he considered branch

10

11

Table 1 (*continued*)

Diagnostic group (International classification of diseases)	Case	Diagnosis	Sex	Gestation	Age (days)	Body weight (kg)	Heart weight (g)	Intimal findings: Extent	Volume bulky	Edema present	Lipid abundant	Cellular infiltration heavy
	44	Meningomyelocele	F	FT	19			+ + +				
	45	Duodenal atresia	F	P	19			+ + +				
	46	Arnold–Chiari malformation	F	FT	28			+ +				
	47	Transposition of great vessels	M	FT	6			+ + + +				
Congenital anomalies	48	Multiple congenital anomalies, heart & gt. vessels	M	FT	31			+ + + +			–	
of the circulatory system	49	Ventricular septal defect tricuspid insufficiency diaphragmatic hernia	F	P	0			+ + + +				
(746 & 747)	50	Pulmonary artery & aorta common stem, one ventricle	M	FT	4			+ +				
	51	Pulmonary stenosis	F	FT	3			+ +				
Certain causes	52	Subdural hemorrhage	M	FT	0	3.1	27	+				
of perinatal	53	Cerebral birth injury edema	M	FT	3	4.5	25	+ +				
morbidity	54	Intracranial birth injury	M	P	0	2.3	18	+ + +				
& mortality (760–779)	55	Subarachnoid & intraventricular hemorrhage	M	FT	1	3.0	34	+ + +				
Birth injury	56	Intraventricular hemorrhage	M	FT	2	4.9	34	+				
without	57	Subdural hemorrhage	M	FT	2	4.1	30	+				
mention of	58	Cerebral anoxia	F	FT	0	2.8	20	+				
cause (772)	59	Cerebral hemorrhage	F	P	8			+ + +				
Hemolytic disease of	60	Erythroblastosis, exchange transfusion	M	P	1	2.9	31	+ +				
the newborn without	61	Erythroblastosis, exchange transfusion	M	P	1	2.7	26	+ + + +				
mention of	62	Erythroblastosis	M	P	5			+ + +				
kernicterus	63	Erythroblastosis	M	FT	0	3.0	22	+				
(775)	64	Erythroblastosis	M	P	0	1.4	15	+			–	
	65	Hydrops	M	FT	1	3.3	24	0			–	
	66	Erythroblastosis	M	P	3	2.1	16	+			–	
	67	Erythroblastosis	F	FT	0			+ +				
	68	Erythroblastosis	F	FT	0	2.5	27	−				
	69	Erythroblastosis	F	FT	1	2.9	19	+				
	70	Hydrops	F	P	2	2.2	22	0				
	71	Erythroblastosis	F	FT	3	3.2	26	− +				
Anoxia &	72	Aspiration of meconium	F	FT	3	3.4	25	+ + + +				
hypoxic	73	Aspiration of meconium	M	FT	1	3.0	33	+ + +				
conditions	74	Aspiration of meconium	F	FT	0			− + +				
not elsewhere	75	Aspiration of meconium	F	P	0	1.5	21	− + +				
classified	76	Aspiration of meconium	F	FT	0	3.1	29	+ +				
(776)	77	Aspiration of meconium	F	FT	1	3.6	22	+				
Aspiration	78	Aspiration of meconium	F	FT	1	4.2	48	+ +				
of content of birth canal (776.0)	79	Aspiration of meconium	F	FT	4			+				
	80	Hyaline membrane disease	M	FT	0			+ − + +				
	81	Hyaline membrane disease	M	P	1			+ + + +				
	82	Hyaline membrane disease	M	FT	1	2.8	19	+ + +				
	83	Hyaline membrane disease	M	FT	1			+ + +				
	84	Hyaline membrane disease	M	FT	1	2.7	30	+ +				
Hyaline	85	Hyaline membrane disease	M	P	1	2.2	15	+ + + +				
membrane	86	Hyaline membrane disease	M	FT	1	2.9	24	+ + + +				
disease	87	Hyaline membrane disease	M	P	2			+				
(776.1)	88	Hyaline membrane disease	M	P	2	1.5	14	+ + +				

Table 1 (*continued*)

Diagnostic group (International classification of diseases)	Case	Diagnosis	Sex	Gestation	Age (days)	Body weight (kg)	Heart weight (g)	Intimal findings: Extent	Volume bulky	Edema present	Lipid abundant	Cellular infiltration heavy
(776.1)	89	Hyaline membrane disease	M	P	3	1.3	12	− +				
	90	Hyaline membrane disease	M	FT	3			+ + + +				
	91	Hyaline membrane disease	M	P	4			+			−	
	92	Hyaline membrane disease	M	P	4			− + + +				
	93	Hyaline membrane disease Maternal diabetes	F	FT	0	3.2	20	+ + + +				
	94	Hyaline membrane disease	F	P	0	1.5	17	+ + + +				
	95	Hyaline membrane disease	M	P	0	2.[illegible]	4	+			−	
	96	Hyaline membrane disease	M	P	0	1.2	14	0			−	
	97	Hyaline membrane disease	M	P	0	1 9	12	+			−	
	98	Hyaline membrane disease	M	P	0	[illegible]0	14	+ +				
	99	Hyaline membrane disease	M	P	0			+ +				
	100	Hyaline membrane disease	M	P	0	2.1	20	+ +				
	101	Hyaline membrane disease	M	P	0	2.0	17	+ + +				
	102	Hyaline membrane disease	M	P	1	1.6	17	+				
	103	Hyaline membrane disease	M	FT	1			+ + +				
	104	Hyaline membrane disease	M	P	1	1.0	9	+				
	105	Hyaline membrane disease	M	P	1	1 4	9	+ +				
	106	Hyaline membrane disease	M	P	1			+ + +				
	107	Hyaline membrane disease	M	P	1	1.4	1	+				
	108	Hyaline membrane disease	M	FT	1	2.7	22	+ + +				
	109	Hyaline membrane disease	M	FT		2.3	[illegible]3	+			−	
	110	Hyaline membrane disease	M	FT	2	2.5	4	+ +			−	
	111	Hyaline membrane disease	M	P		1 6	19	+				
	112	Hyaline membrane disease	M	P	2	1 7	16	+ +				
	113	Hyaline membrane disease	M	P	2	1.8	26	+			−	
	114	Hyaline membrane disease Maternal diabetes	M	FT	2	3.2	26	+ + +				
	115	Hyaline membrane disease	M	P	3	2.1	17	+ +				
	116	Hyaline membrane disease	M	P	4			+ +				
	117	Hyaline membrane disease	M	P	4			+				
	118	Hyaline membrane disease	F	P	0	1.3	19	+ + +				
	119	Hyaline membrane disease	F	P	0			+ +				
	120	Hyaline membrane disease	F	P	1	1 7	1	+				
	121	Hyaline membrane disease	F	P	1	1.6	14	+ +				
	122	Hyaline membrane disease	F	P	1	1 4	15	+				
	123	Hyaline membrane disease	F	P	4			+ +				
Asphyxia of newborn, unspecified	124	Pulmonary atelectasis	M	FT	1	3.6	[illegible]3	+ + + +				
	125	Atelectasis	M	P	0	1.5	1	+				
	126	Atelectasis	M	P	0	1.0	9	+				
	127	Atelectasis	M	FT	1	[illegible]7	25	+				
(776.9)	128	Atelectasis & pulmonary hemorrhage	M	P	1	1 6	17	+				
	129	Atelectasis	M	P	2			+				
	130	Atelectasis	M	P	5			+				
	131	Atelectasis	F	FT	0			+ +				
	132	Atelectasis	F	FT	0			+ + +				
	133	Toxemia of pregnancy placental insufficiency	M	FT	3	1 9	[illegible]5	+ + + +				
	134	Stillborn, retroplacental hemorrhage	F	FT	0	3 1	18	+ + +				
	135	Stillborn, cause unknown, 43 weeks gestation	F	FT	0	3.1	35	+ + +				
	136	Abruptio placentae, Caesarean section	F	FT	1	3 7	31	+ + +				

Table 1 (*continued*)

Diagnostic group (International classification of diseases)	Case	Diagnosis	Sex	Gestation	Age (days)	Body weight (kg)	Heart weight (g)	Intimal findings: Extent	Volume bulky	Edema present	Lipid abundant	Cellular infiltration heavy
All others	137	Stillborn, accidental separation of placenta	M	FT	0			0				
	138	Hemorrhagic disease of newborn	M	FT	0	3.5	23					
	139	Intracerebral hemorrhages, probably anoxic	M	FT	1	3.0	33	+				
	140	Immaturity	F	P	0	0.4	3	+			–	
	141	Cerebral anoxic damage (intrauterine anoxia)	F	FT	0	3.5	37	++				
	142	Cerebral edema & anoxia	F	FT	0	[illegible]9	18	++				
	143	Hemorrhagic disease of new born	F	FT	1	2.8	28	+				
	144	Prematurity	F	P	3	1.6	20	+++				
	145	Meconium ileus	F	FT	19			++				
Ill-defined conditions (780–796) Sudden death	146	Crib death	M		21 (approx)			+++				–
	147	Crib death	M		28 (approx)			+++			–	
All other diagnoses	148	Coxsackie B1 myocarditis, choriomeningitis	M	FT	7			++++				
	149	Pneumomediastinum	M	P	0	2.5	13	+				
	150	Septicemia	M	P	0	[illegible]8	19	++				
	151	Diffuse pulmonary hemorrhage	M	FT	4			+++			–	
	152	Fatty metamorphosis of liver possible glycogen storage disease (Leloir type)	M	FT	9			++++				
	153	Pulmonary hemorrhage	F	FT	0	2.8	23	++				
	154	Diffuse pulmonary hemorrhage	F	FT	4			++				
	155	Pulmonary hemorrhage	F	P	7			+				
	156	Massive hemangio-endothelioma	F	FT	7			++				
	157	Mucoviscidosis	F	FT	26			++++				

Additional histological findings
Case no. 17 macroscopic encrustation (thrombus containing polymorphs, fused with branch pad).
Case no. 27 focal increase in intimal fibrosis.

Table 2. *Relationship of sex and histological findings in intima of coronary arteries in newborn children*

Sex	N of cases[a]	Histological findings in intima (percentages within parentheses): Extent 0	+	++	+++	++++	Volume bulky	Edema present	Lipid abundant	Cellular infiltration heavy
Male	97	5 (5)	28 (29)	22 (23)	22 (23)	20 (21)	25 (26)	19 (20)	7 (9)	5 (5)
Female	60	1 (2)	16 (27)	19 (32)	13 (22)	11 (18)	10 (17)	8 (13)	2 (4)	2 (3)

[a] For lipid, numbers are 80 (male) and 50 (female) only

Table 3 *Relationships of maturity survival time and histological findings in intima of coronary arteries in newborn children*

Survival time in days	Number of cases: Premature (P)	Full term (FT)	Total (TOT)	Histological findings in intima, Extent: 0 P	0 FT	0 TOT	+ P	+ FT	+ TOT	++ P	++ FT	++ TOT	+++ P	+++ FT	+++ TOT	++++ P	++++ FT	++++ TOT
0	19	[illegible]3	42	1	1		7	6	13	6	7	13	4	5	9	1	4	5
1	18	25	43	1	1	2	8	8	16	3	3	6	2	9	11	4	4	8
[illegible] & 3	8	11	19	0	1	1	3	[illegible]	5	3	4	7	1	1	[illegible]	1	3	4
4–7	13	17	30	0	1	1	5	3	8	5	5	10	2	5	7	1	3	4
8–31	5	18	[illegible]3	0	0	0	0	2	2		3	5	1	5	6	[illegible]	8	10
0–31	63	94	157	2	4	6	23	1	44	19	22	41	10	25	35	9	[illegible]	31

site thickenings to be an important precursor of atherosclerosis. Hassler (17), and Rotter and his co-workers (38) who also described cushions in human intracerebral arteries, concluded that these thickenings are physiological rather than pathological. Musculo-elastic branch pads in the kidneys of certain rats are apparently normal anatomical features, but, with development of experimental hypertension many pads undergo hyperplasia and can no longer be regarded as entirely normal (20).

Earlier investigators have supplied abundant evidence that intimal thickenings in the coronary arteries and elsewhere, continue to grow in later life (6, 15 24 25 29 52). Our own current studies of arteries from successive age groups also reveal this growth process quite clearly (19) Because we found thickenings at almost all branch sites in the newborn series, we assume that the growing intimal layer must have advanced from branch sites outwards along the vessel walls. In the marginal zones around thickenings, we regularly found IEL alterations. Elastica changes, with fraying, fragmentation and formation of subendothelial tendrils and fibres (possibly streams of microfibrils), must then have preceded the appearance of intimal MEL cells. The frequent finding of medial disturbances adjacent to altered IEL, and muscle cells, singly and in gr ups, lying within gaps in the elastica suggest the migration of medial cells through the fragmented lamina, to initiate formation of the MEL. The complex remodelling required in a rapidly growing artery especially at bifurcations, can surely not be accomplished without some visible disturbance of the vessel wall. In areas with advanced IEL changes, we often found a complex dovetailing and blending of layers of musculo-elastic tissue in which we could detect no clear line of demarcation between intima and media. The appearance of the wall in such areas suggested an active tissue free from the restraints imposed elsewhere by intact IEL, able to grow in any direction and to remodel itself to meet local requirements.

The positioning of the musculo-elastic pads at bifurcations is strongly reminiscent of the platelet deposition in the extracorporeal shunts employed in experimental work on pigs (30). While the typical arterial cushions in the newborn are clearly not the result of encrustation, the identical location and similar contours of the pads and the deposits seem unlikely to be coincidental because haemodynamic factors, notably turbulence, are considered likely to promote platelet deposition in the shunts, we may speculate that similar forces are involved in the formation of newborn branch cushions.

Regardless of the reasons for the formation of branch site thickenings, their regular presence so early in life suggests that they are normal anatomical structures. And yet, their

olume ulky			Edema present			Lipid abundant			Cellular infiltration heavy		
	FT	*TOT*	*P*	*FT*	*TOT*	*P*	*FT*	*TOT*	*P*	*FT*	*TOT*
1	4	5	0	5	5	1	0	1	1	0	1
3	7	10	3	3	6	2	3	5	0	1	1
2	3	5	2	3	5	0	0	0	0	0	0
3	4	7	1	4	5	0	0	0	0	2	2
1	7	8	2	4	6	1	2	3	1	2	3
0	25	35	8	19	27	4	5	9	2	5	7

massive bulk in some cases is surely indicative of some pathological process. We conclude that coronary branch sites in the newborn infant are normally provided with musculo-elastic pads which are prone to undergo a pathological overgrowth. We may visualize the thickenings in our series as a continuous range from the least to the most massive, encompassing both the normal and the abnormal. We realize, and would like to stress, that because our findings were derived from infants who were sick, they may not reflect accurately the state of the coronary intima in healthy newborn children. The quantity of intimal tissue and the lipid it contains, may be either more or less in healthy babies than in sick ones.

Bulky intimal thickenings, similar to those we observed, can apparently be lethal even in the newborn period. In several reports (2, 12, 21) the death of a newborn infant has been attributed to coronary thickenings resembling those we saw either with or without thrombosis, and all accompanied by myocardial infarction. The continuous range of thickenings found in our series suggest that these fatal cases are not examples of a rare disorder but, rather extreme examples of a common condition.

Speculation on the aetiology of the potentially harmful intimal overgrowth leads us to look closely at the sections and clinical data of those cases in which the intima appeared

Table 4. *Relationship of body weight and histological findings in intima of coronary arteries in newborn children who died during the first 4 days of life*

Body weight (kg)	No. of cases	Histological findings in intima								
		Extent					Volume bulky	Edema present	Lipid abundant	Cellular infiltration heavy
		0	+	++	+++	++++				
Up to 1.7	21	1	11	4	3	2	3	1	0	0
1.8–2.5	20	1	6	5	3	5	5	1	2	0
2.6–3.08	20	0	7	6	4	3	3	3	3	2
Over 3.08	20	2	6	4	6	2	5	5	1	0

Table 5. *Relationship of heart weight and histological findings in intima of coronary arteries in newborn children who died during the first 4 days of life*

Heart weight (gm)	No. of cases	Histological findings in intima								
		Extent					Volume bulky	Edema present	Lipid abundant	Cellular infiltration heavy
		0	–	++	+++	++++				
Up to 16.2	21	1	12	6	1	1	3	1	1	1
16.3–20.9	20	1	6	4	6	3	3	1	1	1
21.0–25.9	20	2	6	4	2	6	7	3	1	0
26.0 and over	20	0	7	5	6	2	3	5	3	0

Table 6. *Inter relationships of histological findings in intima of coronary arteries in newborn children*

Histological findings in intima of coronary arteries		No. of of cases	Additional histological findings in intima of coronary arteries (percentages within parentheses)				
			Extent widespread (+ + +)	Volume bulky	Edema present	Lipid abundant	Cellular infiltration heavy
Extent widespread (+ + + +)	Yes	31	—	4 (77)	16 (56)	4 (13)	3 (10)
	No	1_6	—	11 (9)	11 (9)	5 (4)	4 (3)
Volume bulky	Yes	35	4 (69)	—	16 (46)	5 (14)	3 (9)
	No	122	7 (6)	—	11 (9)	4 (3)	4 (3)
Edema present	Yes	7	16 (59)	16 (59)	—	3 (11)	3 (11)
	No	130	15 (12)	19 (15)	—	6 (5)	4 (3)
Lipid abundant	Yes	9	4 (44)	5 (56)	3 (33)	—	1 (11)
	No	123	_3 (18)	_5 (20)	20 (16)	—	5 (4)
Cellular infiltration heavy	Yes	7	(79)	3 (43)	3 (43)	1 (14)	—
	No	150	79 (20)	4 (16)	3_ (1)	8 (5)	—

oedematous, with pools of ground substance rich in acid mucopolysaccharide separating muscle bundles or forming a subendothelial layer From most arteries, oedematous or not we gained the impression that much of the subendothelial ground substance consisted of blood plasma, often with myriads of lipid droplets like those in the lumen and regularly containing scattered round cells. In most oedematous specimens, an unusually massive inundation of plasma, often accompanied by additional round cells, appeared partially responsible for the intimal swelling. Subendothelial oedema in arteries has been produced rapidly by various experimental means that may have counterparts in the foetus and newborn infant An acute oedematous reaction has resulted from feeding an atherogenic" diet (48) administering adipose tissue lanolin, butter butyric acid, stearic acid, palmitic acid, cholesterol, bradykinin, adrenalin, histamine serotonin angiotensin or inhalations of cigarette smoke or by subjecting animals to traumatic stress (40), or by raising blood pressure by aortic constriction (46) That some of these oedematous reactions result from endothelial damage is suggested by the finding that some of these substances can produce endothelial lesions (4) In pigs fed an atherogenic diet, a rapid oedematous response preceded an intimal proliferation that became evident about 3 weeks later The idea that oedema may promote intimal growth is further supported by the finding of smooth muscle cells, along with blood cells, in the subendothelium (normally cell-free) of arteries in DOCA-hypertensive rats (8) Fractionation of elastic fibres has been described in experimentally induced oedematous reactions in arteries (40) presumably an alteration of this kind in IEL, permitting migration of cells from media to intima, is required before smooth muscle organization of the oedematous intima can take place Focal cellular proliferation located at an IEL gap as in Fig 12, supports the idea that, in human arteries also IEL fractionation is an essential step in the transformation of subendothelial oedema to a more solid musculoelastic tissue

Throughout this study we have been impressed by the histological similarity of the proliferative thickenings we saw and those that develop either spontaneously or experimentally in many animal species (35). Monkeys

(22) swine (10) and rats (47) have all been shown to develop, spontaneously lipid-poor proliferative thickenings closely resembling those we have described. These thickenings, relatively inconspicuous in their natural state undergo a spectacular intensification following ingestion of atherogenic diets. The branch pads described by Stehbens in rabbits also reacted to cholesterol feeding, undergoing IEL altera tion and proliferative change, and spreading, as lipid accumulated in them (44)

We realize, then, that even although lipid was scanty or absent in some of our sections, we should not overlook its possible importance in promoting intimal growth.

The experimental work cited, in conjunction with our findings, suggests that, although we accept a certain amount of intimal prolifera tion as harmless in young children, their ves sels may be as responsive as the experimental animals to a number of factors that may produce intimal oedema, hyperplasia and lipid deposition, even before birth. Deficiencies, as well as excesses, need to be considered: pyridoxine lack, for example, has been reported to stimulate intimal growth in primates (34). We know from numerous studies of animals arteries, that classical atheromata with foam cells and necrosis tend to develop in pre existing foci of proliferation (35). Of special relevance are the findings of Shimamoto and his co-workers (41) who have shown that intimal oedema, followed by atheroma, can be induced in rabbits by administration of certain substances, and also that other substances capable of inhibiting the early oedema are effective anti-atherosclerotics in cholesterol-fed rabbits.

Although the vessels in some of our cases may have been visibly affected by post-natal intensifying factors, the widely varying state of the intima at birth persuades us that ante natal *factors must have played an important* part in determining the condition of the intima. What these *factors* may have been, we can only guess. In itself inconclusive, the finding of excessive thickening in 3 of the 5 cases of congenital heart disease is of interest, and is in keeping with earlier reports of excessive coronary intimal thickening associated with congenital heart disease (3, 4) The possibility that undue intimal thickening may result from maternal rubella has been suggested (1), but we found no history of this condition in our series Excessive intimal thickening has been found to be prevalent in hypertensive children (33) We have no records of blood pressure levels in our series of newborns, so we can only speculate that pressure elevations may on occasion have promoted alterations of the type found in case number 27 (Table 1) these changes, illustrated in Fig. 11 bear a strong resemblance to lesions of experimental hypertension (8 46). Because premature coronary heart disease is often associated with familial hyperlipoproteinaemia type II (11), one would like to know if a positive family history or a suggestive plasma lipid pattern is related to excessive intimal changes even in the newborn infant. Unfortunately we lacked the necessary data to explore these relationships. Because hypoxia has been shown to promote atherosclerosis in cholesterol-fed rabbits (18), we wondered if a history of this condition in the newborn infant might be associated with some visible intimal change. Our data did not suggest this, but were not ade quate for a careful investigation of this point. The possible significance of the bulky oede matous intima in both cases of crib death aroused our interest. Is this the normal condi tion of arteries in healthy babies? Or have these vessels been affected by some disorder associated with crib death?

Some reasons for intimal overgrowth may suggest themselves if we pay attention to cases in which intimal thickenings are absent or unusually scanty and see what they have in common. We have noted the absence of thickenings *in both of* our cases *of* hydrops foetalis and in the case of glucose-6-phosphate dehydrogenase *deficiency* one wonders if because of haemolysis and anaemia in such cases, the passage of blood *through the* vessels may be less

traumatic to the endothelium than the normal flow

Throughout this study an underlying question has always been, "Are these intimal changes related to coronary heart disease in later life?" But perhaps, now that we are becoming better acquainted with the similarity of the very early human changes and recently described experimental lesions, we should be asking the more pertinent question, What 'intensifying factors (or risk factors') have promoted the excessive intimal changes in some of these vessels, so early in life?"

SUMMARY

Coronary arteries of 176 infants up to one month old were dissected unopened from fixed hearts embedded intact, sectioned at close intervals—mostly longitudinally—and examined by light microscope. Musculo-elastic intimal thickenings were regularly found, bulkiest in main trunks and accentuated at branch sites where they formed smoothly rounded pads. Frayed and fragmented elastica underlay and extended beyond all thickenings. Scanty intimal lipid was frequently found, either extracellularly or intracellularly or in both locations. Quantity of intimal tissue varied greatly from case to case, and appeared unrelated to the amount of intimal lipid present Intimal oedema was frequently noted. Histological findings were unrelated to sex, weight gestation period, and survival time. Available clinical data were not related in any definite way to intimal changes. The regular presence of branch pads suggested they were normal anatomical structures, but the finding of massive thickenings in some infants suggested also that the pads are prone to undergo a pathological overgrowth Because of the close histological similarity of the newborn thickenings and those that develop either spontaneously or through use of various atherogenic intensifying factors in many animal species, we speculate that some of these factors may have their counterparts in the earliest events in the life history of the human coronary artery

ACKNOWLEDGEMENTS

We wish to thank Dr Joanna van Belle for work done during the early stages of this investigation, and Miss Ernice Rappaport Mr Brian Watkins and Mr William Wilson for technical assistance. We are grateful to the staff of the Department of Pathology of The Hospital for Sick Children, and to the Ontario Provincial Pathologists and their assistants, for providing all specimens for this study

REFERENCES

1 Campbell, P E., Vascular abnormalities following maternal rubella. *Brit Heart J 27* 134 1967
2 Clapp, J F & Naeye, R. L., Intra-uterine myocardial infarction. *JAMA 178* 1039 1961
3 Constantinides, P & Robinson, M Ultrastructural injury of arterial endothelium. II Effects of vasoactive amines. *Arch Path 88* 106, 1969
4 Dayton, S., Diet and ischemic heart disease: progress in secondary prevention dietary trials. In R. J Jones (ed.): *Atherosclerosis. Proceedings of the Second International Symposium.* Springer-Verlag, New York, Heidelberg and Berlin 1970, p. 577
5 Dock, W The predilection of atherosclerosis for the coronary arteries *JAMA 131* 875 1946.
6. Ehrich, W de la Chapelle, C E. & Cohn, A. E. Anatomical ontogeny man, a study of the coronary arteries. *Amer J Anat 49* 41 1931
7 Enos, W F Holmes, R H. & Beyer J C. Pathology of coronary arteriosclerosis. *Amer J Cardiol 9* 343 1962.
8. Esterly J A. & Glagov S. Altered permeability of the renal artery of the hypertensi e rat an electron microscopic study *Amer J Path 43* 619 1963
9 Fangman, R. J & Hellwig, C. A. Histology of coronary arteries in newborn infants. (Abstract.) *Amer J Path* 23 901 1947
10. Florentin, R. A. & Nam, S. C Dietary-induced atherosclerosis in miniature swine I. Gross and light microscopy observ tions: time of development and morphologic characteristics of lesions. *Exp Molec Path 8* 263 1968
11 Fredrickson, D S. Levy R. I. & Lees, R. S., Fat transport in lipoproteins—an integrated approach t mechanisms and disorders. *New Eng J Med 276* 215 1967
12. Gault M H. & Usher R., Coronary thrombosis with myocardial infarction in a newborn infant. Clinical, electrocardiographic and post-mortem findings *New Eng J Med 263* 379 1960.
13 Gillot P Les altérations histologiques des coronaires foetales et infantiles. *A la Cardiol 17* 143 1962.

14. Glueck, C. J. Heckman, F. Schonfeld, M., Steiner P. & Pearce, W., Neonatal familial type II hyperlipoproteinemia: cord blood cholesterol in 1 660 births. (Abstract.) *Circulation 42*, Suppl. 3 11 1970.
15. Gross, L., Epstein, E. Z. & Kugel, M. A., Histology of the coronary arteries and their branches in the human heart. *Amer J Path 10* 253 1934.
16. Hartroft, W. S. & Porta, E. A., Ceroid. *Amer J Med Sci* 250, 3 4 1965.
17. Hassler O. A systematic investigation of the physiological intima cushions associated with the arteries in five human brains. *Act Soc Med Upsal 67* 35 1962.
18. Helin, P. & Lorenzen, L. Arteriosclerosis in rabbit aorta induced by systemic hypoxia. Biochemical and morphologic studies. *Angiology* 20: 1 1969
19. Jaffé, D. Manning, M. & Hartroft, W. S., Coronary arteries in the earlier decades of man. (Abstract.) *Fed Proc 27* 575, 1968.
20. Jaffé, D. Sutherland L. E., Barker D. M. & Dahl, L. K., Effects of chronic excess salt ingestion: morphologic findings in kidneys of rats with differing genetic susceptibilities t hypertension. *Arch Path, 90* 1 1970.
21. Kemp, E. L., Coronary artery disease in infants, children and young adults. *Review of the literature* and report of cases of thrombotic occlusion in a thirteen-year-old girl and a newborn female infant. Medico-legal Bulletin No. 122, June 1963 Department of Health, Commonwealth of Virginia. Office of the Chief Medical Examiner 404-406 North 12th Street, Richmond 19 Virginia.
22. Kramsch, D. M. & Hollander W. Occlusive atherosclerotic disease of the coronary arteries in monkey (Macaca irus) induced by diet. *Exp Molec Path 9* 1 1968.
23. Kwiterovich, P. O. Levy R. I. & Fredrickson, D. S., Early detection and treatment of familial type II hyperlipoproteinemia. (Abstract.) *Circulation, 42* Suppl. 3 11 1970.
24. Levene, C. I. The early lesions of atheroma in the coronary arteries. *J Path Bact 72* 79 1956.
25. Lober P. H., Pathogenesis of coronary sclerosis. *Arch Path, 55* 357 1953
26. McManus, J. F. A. & Mowry R. W. *Staining Methods Histologic and Histochemical* Paul B. Hoeber Medical Division of Harper and Row New York, 1960
27. Minkowski, W. L. The coronary arteries of infants. *Amer J Med Sci 214* 623 1947
28. Moon, H. D. & Rinehart, J. F. Histogenesis of coronary arteriosclerosis. *Circulation, 6* 481 1952.
29. Moon, H. D. Coronary arteries in fetuses, infants and juveniles. *Circulation 16* 263 1957
30. Murphy E. A. Rowsell, H. C. Downie, H. G., Robinson, G. A. & Mustard, J. F. Encrustation and atherosclerosis the analogy between early in vivo lesions and deposits which occur in extracorporeal circulations. *Canad Med Ass J 87* 259 1962
31. Neufeld, H. N. Wagenvoort, C. A. & Edwards, J. E. Coronary arteries in fetuses, infants, juveniles and young adults. *Lab Invest 11* 837 1962.
32. Oppenheimer E. H. & Esterly J. R., Some aspects of cardiac pathology in infancy and childhood. II. Unusual coronary endarteritis with congenital cardiac malformations. *Bull Hopkins Hosp 119* 343 1966.
33. Oppenheimer E. H. & Esterly J. R., Cardiac lesions in hypertensive infants and children. *Arch Path 84* 318 1967
34. Rinehart, J. F. & Greenberg, L. D., Pathogenesis of experimental arteriosclerosis in pyridoxine deficiency. With notes on similarities to human arteriosclerosis. *Arch Path 51* 12, 1951
35. Roberts, J. C., Jr. & Straus, R. (eds.): *Comparative Atherosclerosis. The Morphology of Spontaneous and Induced Atherosclerotic Lesions in Animals and Its Relation to Human Disease* Paul B. Hoeber Medical Division of Harper and Row New York, 1965
36. Robertson, J. H. The significance of intimal thickenings in the arteries of the newborn. *Arch Dis Child 35* 588, 1960.
37. Robertson, J. H., Stress zones in foetal arteries *J Clin Path 13* 133 1960.
38. Rotter W. Wellmer H. K., Hinrichs, G. & Muller W. Zur Orthologie und Pathologie der Polsterarterien (sog. Verzweigungs- und Spornpolster) des Gehirns. *Beitr Path Anat 115* 253 1955
39. Schornagel, H. E. Intimal thickening in the coronary arteries of infants. *Arch Path 62* 427 1956.
40. Shimamoto, T. The relationship of edematous reaction in arteries to atherosclerosis and thrombosis. *J Atheroscler Res 3* 87 1963
41. Shimamoto, T. Experimental study on atherosclerosis—an attempt at its prevention and treatment. *Acta Path Jap 19* 15, 1969
42. Singer D. B. Histology of the coronary arteries in congenital heart disease. *Cardiovasc Res Cent Bull 2* 106, 1964
43. Stehbens, W. E., Focal intimal proliferation in the cerebral arteries of man. *Amer J Path 36* 289 1960.
44. Stehbens, W. E. The renal artery in normal and cholesterol-fed rabbits. *Amer J Path 43* 969 1963
45. Stehbens, W. E., Intimal proliferation and spontaneous deposition in the cerebral arteries of sheep and steers. *J Atheroscler Res, 5* 556, 1965
46. Still, W. J. S., The early effect of hypertension on the aortic intima of the rat. An electron microscopic study *Amer J Path 51* 721 1967
47. Thomas, W. A., Jones, R., Scott, R. F. Morrison, E. Goodale, F. & Imai, H., Production of early atherosclerotic lesions in rats characterized by proliferation of modified smooth muscle cells *Exp Molec Path 2 Suppl. 1* 40, 1963
48. Thomas, W. A., Florentin, R. A., Kim, D. N. Jones, R. M. & Lee, K. T. Preproliferative phase

of atherosclerosis in swine fed cholesterol. *Arch Path 86* 6.1 1968.

49 Turpeinen, O., Control of atherosclerosis, progress in primary diet trials. In R. J. Jones (ed.) *Atherosclerosis: Proceedings of the Second International Symposium* Springer Verlag, New York, Heidelberg and Berlin 1970 p. 572.

50. United States Department of Health, Education and Welfare: *International Classification of Diseases 8th Revision, Adapted for Use in the United States.* National Center for Health Statistics. Public Health Service Publication No. 1693 Washington, 1967

51 Vlodaver Z., Abramovici, A., Neufeld H. N. & Liban, E., Coronary arteries in Yemenites. *J Atheroscler Res* 7 161 1967

52. Vlodaver Z. & Neufeld, H. N., The musculoelastic layer in the coronary arteries. A histologic and hemodynamic concept. *Vasc Dis* 4 136, 1967

53 Vlodaver Z., Kahn, H. A. & Neufeld, H. N The coronary arteries in early life in three different ethnic groups. *Circulation* 39 541 1969

54. Wilson W., Unpublished method. The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada.

55 Wolkoff K. Über die Atherosklerose der Coronararterien des Herzens. *Beit Path Anat* 82: 555 1929

56. World Health Organization. *Classification of Atherosclerotic Lesions, Report of a Study Group.* In WHO Technical Report Series No. 143 Geneva, 1958.

57 World Health Organization. *International Work in Cardiovascular Diseases* 1959–1969 WHO Geneva, 1969

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

161. Palmén, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W. Focal Spike Discharges in Children, a Longitudinal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margot, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 28.— 1966
172. *Festschrift in Memory of Constantin Chevremis.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Oesophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Pettersson, Per Ove, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Miettinen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 28.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress, Bergen,* 1967. Sw. kr. 15.— 1967
178. Kjellberg, Ivan, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 28.— 1968

Koch, Gösta, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968

Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968

183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Elsa, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1968
188. Meeuwisse, Gunnar W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1968
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Koivikko, Antti, Cardiovascular Responses of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kumento, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969
197. Kamis, Rava, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 20.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Sanjur, Diva M., Cravioto, Joaquin, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 25.— 1970
201. Sutherland, Lynette E., Hartwell, Phyllis, Rahe, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kristian, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 3–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 35.— 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admission. Sw. kr. 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Hakulinen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971
214. Samuelson, Göran, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 25.— 1971
215. Bergmann, Stella Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped Children. Sw. kr. 25.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposia,* Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. Sw. kr. 35.— 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 35.— 1971
219. Jaffé, Doris, Hartwell, Stanley, Manning, Mary and Dees, Gemma, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. Sw. kr. 25.— 1971

Price Swed. kr 25.—

Printed in Sweden by Almqvist & Wiksells Boktryckeri AB Uppsala

710871

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 221 1971

A COMPARATIVE STUDY OF ADOPTED CHILDREN, FOSTER CHILDREN AND CHILDREN IN THEIR BIOLOGICAL ENVIRONMENT BORN AFTER UNDESIRED PREGNANCIES

BY MICHAEL BOHMAN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

*From the Child Psychiatric Department of Karolinska Institutet
at St Görans Hospital (Head, Professor Sven Ahnsjö) Stockholm
and the Child Welfare Committee of Stockholm
(Head Director Karl-Erik Granath)*

A comparative study of adopted children, foster children and children in their biological environment born after undesired pregnancies

by

MICHAEL BOHMAN M.D

STOCKHOLM 1971

Translated by
PATRICK HORT

Tryckeri Balder AB Stockholm 1971

CONTENTS

INTRODUCTION 5

MATERIAL AND DROP-OUT 5

AIMS OF THE STUDY 7

METHODS, SOURCES OF INFORMATION AND CLASSIFICATION 7
Registers, School study Controls, Statistical methods

THE BIOLOGICAL BACKGROUND 8
Biological mothers, Biological fathers, Registered criminality
Registered abuse of alcohol, Sex differences

THE CHILDREN AT BIRTH 10
Perinatal complications, Twins, Malformations, Institutional care

THE CHILDREN AT FOLLOW UP 12
Adjustment in school, The children's adjustment scores, Certain behavioural and other characteristics of the subjects compared with their same sex classmates, School placement, School marks, School problems and nervous disturbances according to the school health card

ANALYSIS OF THE RESULTS 24
Adjustment scores related to background variables, Complicated pregnancy and birth related to school adjustment, Maternal deprivation, "The social heredity" The importance of criminality and abuse of alcohol in the biological background, Discussion

GENERAL DISCUSSION AND SUMMARY 33

ACKNOWLEDGEMENTS 36

REFERENCES 37

INTRODUCTION

The study presented in this paper concerns various aspects of the way in which children whose conception was not desired have developed in and adjusted to their biological or non-biological environment. It also includes an analysis of the extent to which various background factors may have influenced these children's development. The investigation was based on a group of women who in the mid-Fifties reported to the Stockholm Adoption Agency that they wished to have their child adopted. These mothers were without exception in a difficult social and psychological situation. They were mostly young and single, with very limited means for taking care of the child; about half of them already had an older child to look after. But the primary reason for wishing to have the child adopted seems to have been lack of support from the father of the child or from their own family. The majority of the children were in fact placed in adoptive or foster homes but a substantial number of the mothers, instead of following up their application to the Adoption Agency, brought up the child themselves.

Children born out of wedlock are known to run a greater risk than other children of developing nervous symptoms or behavioural disturbances and they are also over-represented in so-called problem populations (Illsley 1967). One of the reasons for this seems to lie in the social disadvantages experienced by many unmarried or separated mothers making it difficult for them to look after the child and give it a secure background. It has also been assumed that physical and mental strains during pregnancy affect the unborn child and involve a risk of developmental disturbances and difficulties of adjustment (Stott, 1969 and others). A further suggestion is that children born out of wedlock have a heavier genetic "burden" than other children.

The children of unmarried or separated mothers, however, form such a heterogeneous group that sweeping characteristics are hardly meaningful. As a rule the unmarried mother does not remain unmarried or "single" (Berfenstam & Villner 1966). The implications of illegitimate birth seemingly vary between different social and demographic strata. Illegitimate children, although they may be conceived unintentionally, are seldom truly unwelcome. Most of them are made legitimate by the parents' marriage or else they are included in a new family group. Only a small proportion of children born out of wedlock grow up with a solitary parent and still fewer grow up with adoptive or foster parents (Berfenstam & Villner 1966). The mothers of children whose conception was unintentional and undesired thus appear to regard adoption as a last resort (Höök, 1963, Oyen, 1966, Bohman, 1970 and others) and most women in our culture seem to prefer abortion to adoption. Once the child has been born, moreover, the great majority of mothers prefer to look after it themselves rather than give it away (Höök, 1963). Whether the child is left for adoption or not appears to depend on external, material circumstances as well as on emotional motives (Vincent, 1961).

MATERIAL AND DROP-OUT

A follow-up study of adopted children and their families was started in 1965 at the Child Welfare Committee of Stockholm City. In order to obtain a representative material, data were obtained on two year groups of children—giving a total of 624 children—whose mothers had applied to the Committe to have their child adopted just

before or after it was born. Of these 624 children, who constitute the primary series in this study only 168 were placed directly in adoptive homes through the Committee's Adoption Agency in nearly every case before they were 1 year old. These children have been the subject of a separate study that also covered the adoptive family and the biological parents (Bohman, 1970) The other children in the primary series were looked after in various ways after about a decade roughly a third were living in their biological environment (usually with their biological mother) and the others were either with foster parents or else they too, had been adopted. The placement of the children about 10—11 years after birth is shown in absolute figures in *Table 1*

The circumstances under which the children in the primary series had grown up were highly varied and it was clear from the start that the study should permit comparisons between the groups in order to assess the outcome of different placements. For this reason the initial study concerning adoption, which concentrated on the 168 children handled by the Adoption Agency was extended in certain respects to include a large proportion of the other children in the primary series.

The study reported here comprises a total of 492 children (266 boys and 226 girls) from the 624 in the primary series, divided into three groups with respect to their placement. The size of the groups, is shown in *Tabl 2* The children in *Group I* (adopted children placed via the Adoption

Table 1 *Placem nt of the 624 child en in the primary eri at follo up appro 10—11 years after their birth*

Current placement	No of children
Adopted through Stockholm Adoption Agency	168
Adopted, but not through the Stockholm Agency	126
In foster home	77
With biological mother	228
At an institution	3
Some other placement	6
Dead	14
Unknown	2
Total	6 4

Table 2 *Composition f the bject group*

Group	No. of children
I Adopted at an early age	163
II Living with biological mother	205
III Other adopted and foster children	124
Total	492

Agency) were, as mentioned, placed in their adoptive home before their first birthday usually after a stay at an infants home. The great majority of these adoptive families lived in sizeable urban communities and their social and economic standards were considerably higher than those of parents in the average population. The children in *Group II* were living with their biological mother at the time of the follow up but they form a heterogeneous group in terms of childhood background and social environment. In approximately 30 % of these cases the mother was living with the biological father Only about a third of these children had stayed at an infants home, the others being cared for by the mother from soon after birth. The majority of these children and their mothers were living in sizeable urban communities. The children in *Group III* (other adopted and foster children) were entirely separated from their biological environment at the time of the follow up. This group may be regarded as a negative selection from the primary series, in that many of the children were considered at birth, or while at an infants home, to be difficult to place on account of retarded development, poor heredity or somatic complications. It often took longer to place these children in their ultimate home environment than it did the other children in this study more than half of them spent over nine months at an institution before being placed. Their relatively late placement may also have to do with the biological mothers inability to reach a decision concerning placement. Most of the children in this group in contrast to the other two, lived in small communities or out in the country Their adoptive or foster parents were also older on the average than the adoptive parents in *G oup I* and had a lower education or occupational status (see *Table 3*)

Table 3. *Occupational category of adoptive fathers (British classification, H. M. S. O. (1951)). Comparison between adopted children in Groups I and III. Percentage distribution.*

Occupational category	Group I (N=168)%	Group III (N=123)%
Unskilled	4	7
Partly skilled	5	16
Skilled	23	32
Intermediate occupations	41	40
Professional	27	5
Total	100	100

There was not time to include the greater part of one year group (79 children) that would otherwise have belonged to *Group III* but this selection is of no importance for the problems considered here. The drop-out in other respects was as follows dead 15 abroad or address unknown 27 other placement (with relatives) 6, mentally retarded and not attending school 1. in 5 cases school marks were obtained but no interviews with teachers. Information about school marks was not obtained in a few cases but very little information was missing in other respects and this was of no importance for the results.

AIMS OF THE STUDY

The study was designed to penetrate the following questions

1. Are there differences in school adjustment and school results (marks) between the children in Groups I—III and the children in other representative groups?
2. Are there differences in school adjustment and school results (marks) between the children in each of the Groups I, II and III?

In addition to these group comparisons, which should give a general impression of what the different types of placement have meant for the development of these children, the study was also designed to assess the importance of certain background factors for the children's adjustment.

Starting from theories that attempt to explain behavioural variations among children (for a discussion see my previous study—Bohman, 1970) I worked on the assumption that the children's adjustment and school results could be associated with hereditary as well as with earlier environmental factors. Hypotheses were set up concerning the following factors

1. Pre and perinatal factors.
2. Institutional care during infancy
3. The socio-economic circumstances of the biological parents up to the birth of the child.
4. The existence of social or mental insuffiency among the biological parents before the child was born.
5. Registered criminality or abuse of alcohol among the biological parents up to the time of the follow-up.

When these hypotheses were tested on the adopted children in my earlier study they remained largely unverified. Neither pre and perinatal factors, the social background of the biological parents nor institutional care was associated significantly with the children's adjustment.

Some of these hypotheses will be tested again in the present study since it is conceivable that the importance of these background factors varies with the environment in which the child grows up.

Criminality among the biological parents, for instance, is a background factor that presumably differs in its implications for the children who live in a protected social environment (e.g. in an adoptive home) compared with those living in less secure circumstances (e.g. with a solitary mother or if she marries, as a stepchild). It has also been suggested that complications during pregnancy or birth may affect the ability of children to adjust if they grow up under adverse social conditions (Illsley 1967 Werner et al, 1967)

METHODS, SOURCES OF INFORMATION AND CLASSIFICATION

Registers

Information concerning the biological parents ages, marital status, education, occupations and housing conditions at the time of the child's birth was obtained from the records of the Adoption

Agency The biological father had not been identified—and consequently no information about him was available—in 10 % of the cases. Data on marital status and number of children at the time of the follow-up were obtained from the national census records. Information concerning registered criminality and offences under the Temperance Act was obtained by special permission from the Criminal Register and the Excise Board Register respectively Certain information on adoptive and foster parents was also obtained from registers. The birth records of all the children were kindly placed at my disposal for data on the weight at birth and perinatal conditions.

School study

The schools provided copies of the children's reports (usually from the 3rd school year) and school health cards. The children's class teachers were interviewed by telephone in accordance with a special questionnaire. The methods used in this part of the investigation have been reported in my earlier study At the time of the interviews most of the children were attending the 4th form and were roughly 11 years old. The information obtained from the teachers was used to classify the children into five degrees of "symptom loads" or adjustment scores with respect to their adjustment to the school situation. This classification, which has also been used by Jonsson & Kälvesten (1964) in their study on 222 Stockholm boys, is as follows

Adjustment score 1 Symptom free
No symptoms at all or the mildest form of either nailbiting or difficulties in reading and writing or similar

Adjustment score 2 Slight symptoms
One or more symptoms of a type and degree that do not disturb the child's surroundings, e.g. slight sensitivity ("coping well with symptoms")

Adjustment score 3 Moderate symptoms
One or more symptoms which clearly set the child apart but do not constitute a pressing problem ("coping with symptoms") no acute need for treatment. Example children who manage well in a special class.

Adjustment score 4 Problem children
Several symptoms of a type and degree that make immediate help necessary e.g. at a child guidance clinic or some other specialist advice.

Adjustment score 5 Institutional cases
The child too disturbing to remain in its natural environment, requiring treatment at a special institution.

Controls

From the catalogue of class marks, a classmate of the same sex was selected at random to serve as a control for each subject. When the time came to interview the teachers, only 317 controls were still to hand because families had moved and classes had been reorganized between the third and fourth school years. Tests showed, however that this selection did not significantly affect the representativeness of the control series.

Statistical methods

Conventional statistical methods were used for processing the material (Blalock, 1960, Siegel, 1965) Non parametric methods were used as a rule, such as the X^2-test when comparing two independent groups. In those instances where the methods of measurement permitted interval scales, e.g school marks, use was made of *t* tests. A result is described as significant if $p < 0.05$ p being calculated for a one-tailed test in the case of directed hypotheses (noted in the tables and text)

THE BIOLOGICAL BACKGROUND

Biological mothers

The biological mothers were unmarried or solitary as a rule (approx. 85 %) when their child was born. About 60 % were under 25 and 20 % were under 20 About half of them had given birth to one or several children before. Their social and economic circumstances were characterized by most of them having no home of their own (approx.

70 %) an unqualified occupation and inadequate education. In these respects, however there is little difference between the groups (I, II and III).

At the time of the follow-up about a decade after the child's birth, approximately 20 % of the mothers were still unmarried according to the national census, 60 % were married, 18 % divorced, 1 % widows and 1 % had died. Comparisons between the mothers in the three groups (I—III) reveal only minor non-significant differences in the breakdown by marital status. The mother was married with the child's father in 17 % of the cases not unexpectedly this was most common in Group II (30 %) where the child was living with its biological mother while it was least common in Group I (9 %) where the children had been placed via the Adoption Agency.

About 40 % of the mothers in the entire series had not had any more children after the birth that caused them to apply to the Adoption Agency: about a third had had one more child and a quarter two children or more. There were no differences between the mothers in the three groups with respect to the number of children born during the observation period.

Entries in the Criminal Register were found for 6 % of the biological mothers, with substantial differences between the three groups 4.9 % in Group I, 3.9 % in Group II and 10.5 % in Group III. These frequencies are considerably higher than one would expect to find in groups of women selected at random.

The register of offences under the Temperance Act kept by the Excise Board contained entries on 4.0 % of the mothers in the entire series and here, too, there was a considerable variation between the groups 3.0 % in Group I, 1.5 % in Group II and 9.7 % in Group III. These frequencies are also substantially higher than one would expect to find a normal population. According to a government report (S.O.U. 1951: 43) only 0.3 % of women in urban populations occur in the register of the Excise Board. The relatively high incidences of criminality and abuse of alcohol point to a negative selection. The present figures are in the same range as those found by Jonsson (1967) for the mothers of delinquent boys at institutions criminality 4.6 % and abuse of alcohol 7.0 %.

Biological fathers

The biological fathers had told the Adoption Agency relatively little about themselves, so that the pictures of this group is less complete than for the mothers. Furthermore, as already mentioned, no information at all was available in the 10 % of cases where the father had not been identified. Of the identified fathers, just over half were unmarried, a quarter married and the remainder divorced or separated. They were younger on the average and had a lower education than a representative group of fathers.

Registered criminality

At the time of the follow-up entries on one-third of the identified biological fathers were found in the *Criminal Register*. This is a substantial overrepresentation, the figure to be expected for a representative group of men being about 10% (Jonsson & Kälvesten, 1964, Husén, 1969). Registered criminality also differed somewhat, though not significantly between the three groups, being lowest (27 %) in Group I, somewhat higher (34 %) in Group II and highest (40 %) in Group III (see *Table 4*). It should be noted that most cases concerned recurrent criminality frequently combined with offences under the Temperance Act.

Registered abuse of alcohol

Altogether 37 % of the identified biological fathers were traced in the Excise Board's register of

Table 4. *Entries in the Criminal Register among known biological fathers. Percentage distribution.*

Registered criminality	All fathers (N=434) %	Group I (N=146) %	Group II (N=183) %	Group III (N=105) %
Yes	33	27	34	40
N	67	63	66	60
Total	100	100	100	100

Table 5. R gistered ff nd the T mpe an ct am g kno biolog al fath s Per tag distribution

Registered abuse of alcohol	All fathers (N=434) %	Group I (N=146) %	Group II (N=183) %	Group III (N=105) %
Yes	37	26	39	48
No	63	74	61	52
Total	100	100	100	100

offences under the Temperance Act. This may be compared with a figure of 18 % for the fathers in the representative study by Jonsson & Kälvesten. In the present case there were substantial differences between the groups, with incidences of 26 % in Group I, 39 % in Group II and 48 % in Group III (significant difference, $p < 0.01$). There was thus a moderate *but* clear over representation among the fathers of the children placed via the Adoption Agency (Group I) and a very much widespread abuse of alcohol among the fathers of adoptive and foster children in Group III while the fathers in Group II had an intermediate frequency *(Table 5)*

Sex differences

For the series as a whole, no significant difference between boys and girls was found with respect to criminality and abuse of alcohol among their biological fathers. When the three groups were analyzed separately however differences were found as follows.

Group I Registered criminality was rather more common among the boys *fathers than the girls* (29 6 % and 24.6 % respectively) Offences under the Temperance Act, on the other hand, were rather more common among the fathers of girls (27 7 % and 24 7 % respectively)

Group II Here there was a *clear difference* between the boys and the girls fathers, only 26 % of the former occurring in the Criminal Register *compared* with 43 7 % of the latter This difference can hardly be attributed simply to chance. A possible element of selection may lie in the circumstance that the biological mothers who considered the idea of retaining their child were more doubtful if the biological father had a criminal record or *problems with alcohol and that this doubt was* greater if the child was a boy as opposed to a girl. In other words, the mothers in such cases may have feared that their son would grow up with the same problems as the father Indeed, at the time of the child s birth, only 17 7 % of the fathers of the boys who ended up in Group II were entered in the Criminal Register compared with 34.5 % of *the girls fathers,* the corresponding *figures* for offences under the Temperance Act being 34.4 % and 43 7 %

Group III Registered criminality was somewhat more common among the boys fathers compared with the girls (41 4 % and 38.3 % respectively) Offences under the Temperance Act were also more widespread among the fathers of the boys. *In this group, therefore, the trend is the opposite* of that in *Group II* where criminality and abuse of alcohol were more common among the fathers of the girls.

Boys account for 54 % of the total series. The proportion of boys in Group I is 55 % in Group II 52 % and in Group III 56 % Although these differences are slight, they may reflect a tendency *for the biological mothers to be rather more prone* to retain a girl as opposed to a boy

THE CHILDREN AT BIRTH

Perinatal complications

Information concerning pregnancy and birth was obtained from the hospitals maternity records, *which were available in every case. About 6 % of* the children were born prematurely i.e. their weight at birth was less than 2 500 g This is a relatively low figure considering that it concerns illegitimate or unwelcome pregnancies. The incidence in Group III was somewhat higher than in the other two groups. Pathological findings during pregnancy had been recorded in about 35 % of the cases *(Table 6)* In the majority of cases the complication involved some form of toxemia (a group that also includes cases where

Table 6. *Complications during pregnancy. Percentage distribution*

Complications during pregnancy	All mothers (N=488) %	Group I (N=163) %	Group II (N=201) %	Group III (N=124) %
Yes	35	31	37	39
No	65	69	63	61
Total	100	100	100	100

Incomplete information in 4 cases

the records simply note a diastolic blood pressure ≥90 mm and/or a systolic pressure ≥140 mm). It will be seen from the table that the frequency of complications differed somewhat between the three groups, being lowest (31 %) for the children in Group I and highest (39 %) for those in Group III. Complications in connection with birth had been registered in about 10—15 % of the cases. The lack of a comparable control series makes it difficult to determine whether the frequency of perinatal complications was abnormally high but this does seem to have been the case. In particular toxemia as defined above appears to have been uncommonly frequent, which may have to do with

Table 7. *Complications during pregnancy and birth. Total series (N=624). Per cent*

1	*"Toxemia"*		
	a. Hypertension (≥90 mm diast. or ≥140 mm syst. blood pre.) + proteinuria and/or increase by 20 % of normal weight (pure toxemia)	8.3	
	b. Hypertension alone	7.0	21.3
	c. Increase by 20 % of normal weight	4.0	
	d. Proteinuria (at least twice) alone	2.0	
2.	*Hemorrhages ante partum*		4.3
3.	*Other complications during pregnancy* (narrow pelvis, premature rupture of fetal membranes, jaundice, Rh sensitization, pruritus, hyperemesis, anemia, VOC, intoxications connected with attempted suicide, gonorrhea, etc.)		14.3
4.	*Abnormal position of fetus* (incl. breech presentation		6.3
5.	*Assisted delivery* (forceps, caesarean section, suction cup etc.)		3.2
6.	*Asphyxia* (perinatal)		5.5

the biological mothers having been subjected to unusually great social and psychological pressure during the pregnancy. The complications during pregnancy and birth that were noted in the majority records are summarized in *Table 7*.

Twins

The 624 children in the primary series included 12 who were born as twins. The twins were the same sex in five pairs out of the six, girls in three and boys in two. One of the girl twins died as an infant and her sister was placed in an adoptive home. In three other pairs, the twins were placed in different homes: in different adoptive or foster homes in the case of two pairs and in the biological and a foster home respectively in the third. Another pair (girls) lived with the biological mother and the sixth pair (a boy and a girl) in the same adoptive home. There was no possibility of determining whether the same-sex pairs were monozygotic or dizygotic.

Malformations

Malformations were noted at or just after birth in 20 of the 624 children in the primary series, an incidence of 32.1 0/00. This may be compared with a figure of 10.6 0/00 reported by Källén & Winbergh (1968) in a sizeable representative series of newborn children in Sweden. The difference between these frequencies is significant, $p < 0.001$ ($X^2 = 19.39$). Further cases of malformation were observed later and there were four children with severely impaired hearing, probably from birth and possibly indicating a perinatal injury. These frequencies are no doubt minimum figures and should be judged in the light of the positive selection involved in the present series—the mothers usually applied to the Adoption Agency relatively late in their pregnancy, which tends to exclude late abortions as well as certain premature children, i.e. groups where malformations are usually most common. This is also indicated by the observation, mentioned above, that the frequency of premature birth was relatively low (6 %) considering the mother's exposed situation. It is therefore probable that the series includes an excessive incidence of

Table 8. *Duration of stay at infant's home. Percentage distribution*

Distribution of stay (months)	All groups (N=491) %	Group I (N=163) %	Group II (N=205) %	Group III (N=123) %
None	33	4	64	17
0—2	7	9	6	6
3—5	20	43	7	11
6—8	19	34	12	12
9—11	14	9	7	33
12—14	7	1	4	21
Total	100	100	100	100

malformations, possibly reflecting the social and psychological stress under which the mothers lived during the pregnancy (Stott, 1969 and others) It is possible that some of the malformations reflect attempts to provoke an abortion in the early weeks of pregnancy

Institutional care

Before their final placement, 67 % of the children were cared for at infants homes, where they were placed as a rule straight from the maternity clinic. As will be seen from *Table 8* as many as 96 % of the children in Group I stayed at infants homes, followed by 83 % in Group III but only 36 % in Group II

Nearly all the children stayed at infants homes in the Stockholm area, where the standard in the mid Fifties was relatively high. The staff ratio was also comparatively high, 2—3 children per nurse, and the children no doubt received good material care. Even so, nurses may have been changed frequently the environment may have been too like that of a hospital and probably did not suffice to give the children a sufficient emotional stimulus.

THE CHILDREN AT FOLLOW-UP

Adjustment in school

Hypotheses

I adopted the hypothesis that the children in Group I would display the best adjustment and the best school results compared with the other two groups because, besides representing a positive selection, these adopted children had been placed in homes selected and investigated by the Adoption Agency prior to the placement. I also adopted the hypothesis that adopted children should be less well adjusted than controls boys less than girls.

I also hypothesized that the children in Group III would display poorer adjustment and poorer school results than the other groups including the controls, partly because it included a higher proportion of children with somatic and hereditary handicaps but also because the children in this group had stayed longer than other children at infants homes while waiting for their final placement.

Finally I hypothesized that the children in

Table 9 *Group I adopted children. Adjustment in school compared with class controls*

Adjustment scores	Boys				Girls			
	Subjects		Controls		Subjects		Controls	
	N=90	%	N=50	%	N=73	%	N=44	%
1	26	29	28	56	45	62	33	75
2	13	15	7	14	11	15	4	9
3	31	34	9	18	9	12	5	11
4	18	20	6	12	8	11	2	5
5	2	2	0	0	0	0	0	0
Total	90	100	50	100	73	100	44	100
	A		A_1		B		B_1	

Diff A—A_1 $X^2=10.97$ (3 df) $p < 0.01$ (one-tailed test)
Diff A—B $X^2=20.94$ (3 df) $p < 0.001$

Group II, having grown up with their biological mother would display an intermediate level of adjustment compared to the other two groups. Since some of these children would presumably encounter problems on account of their mother's difficult social and psychological starting point, one could expect a somewhat higher incidence of maladjustment in this group compared to controls.

The children's adjustment scores

The results of the interviews with teachers were used, as already mentioned (see p. 8) to classify the children by adjustment scores. The inter group comparisons have been made with directed hypotheses, so that p has been calculated for one-tailed tests.

Group I Adopted children placed through the Adoption Agency (Table 9)

In Group I, 24 % of the adopted boys were classified as "problem cases" that is they were definitely maladjusted in the school situation and, according to my criteria, in need of assistance (adjustment scores 4—5). A further 34 % displayed clear symptoms or behavioural disturbances but were not considered to be in direct need of assistance or treatment (adjustment score 3) and only 44 % of the boys were judged to be almost or *entirely free from symptoms or disturbances* (adjustment scores 1—2). The frequency of problem cases in the control group was definitely lower (12 %) and 70 % were almost or entirely free of symptoms. The differences between the adopted boys and their controls with respect to adjustment are significant ($p < 0.01$ one-tailed test). The adopted girls also had a higher proportion of problem cases than their controls (11 % as against 5 %) but the differences were not so pronounced and neither were they significant. On the other hand, the differences in adjustment between the adopted boys and the adopted girls are significant ($p < 0.001$)

Group II Children with their biological mother (Table 10)

Of the boys who were living with their biological mother 20 % were problem cases compared with 12 % of the controls. Boys with moderate symptoms were also more common (26 %) in this group compared with their class controls. The difference is not fully significant, $p < 0.1$ indicating that the boys in this group cope better than the adopted boys in relation to their controls. A somewhat higher proportion of the girls living with their mother were also classified as problem cases compared with the controls (9 % as against 6 %) but the difference may be due to chance in five cases out of ten. On the other hand there is a significant difference between the adjustment of the boys and the girls in Group II ($p < 0.01$). This group included one child with defective hearing and retarded development who at times was cared for at an institution.

Table 10. *Group II children living with biological mother. Adjustment in school compared with class control*

Adjustment scores	Boys: Subjects N=107	%	Boys: Controls N=61	%	Girls: Subjects N=98	%	Girls: Controls N=66	%
1	33	31	27	44	49	50	36	55
2	25	23	16	26	15	15	14	21
3	28	26	11	18	25	26	12	18
4	19	18	7	12	8	8	4	6
5	2	2	0	0	1	1	0	0
Total	107	100	61	100	98	100	66	100
	A		A		B		B	

Diff A—B $X^2 = 10.22$ (3 *df*) $p < 0.01$ (one-tailed test)

Table 8. *Duration of stay at infants' homes. Percentage distribution*

Distribution of stay (months)	All groups (N=491) %	Group I (N=163) %	Group II (N=205) %	Group III (N=123) %
None	33	4	64	17
0—2	7	9	6	6
3—5	20	43	7	11
6—8	19	34	12	12
9—11	14	9	7	33
12—14	7	1	4	21
Total	100	100	100	100

malformations, possibly reflecting the social and psychological stress under which the mothers lived during the pregnancy (Stott, 1969 and others). It is possible that some of the malformations reflect attempts to provoke an abortion in the early weeks of pregnancy.

Institutional care

Before their final placement, 67 % of the children were cared for at infants' homes, where they were placed as a rule straight from the maternity clinic. As will be seen from *Table 8*, as many as 96 % of the children in Group I stayed at infants' homes, followed by 83 % in Group III but only 36 % in Group II.

Nearly all the children stayed at infants' homes in the Stockholm area, where the standard in the mid Fifties was relatively high. The staff ratio was also comparatively high, 2—3 children per nurse, and the children no doubt received good material care. Even so, nurses may have been changed frequently, the environment may have been too like that of a hospital and probably did not suffice to give the children a sufficient emotional stimulus.

THE CHILDREN AT FOLLOW UP

Adjustment in school

Hypotheses

I adopted the hypothesis that the children in Group I would display the best adjustment and the best school results compared with the other two groups because, besides representing a positive selection, these adopted children had been placed in homes selected and investigated by the Adoption Agency prior to the placement. I also adopted the hypothesis that adopted children should be less well adjusted than controls, boys less than girls.

I also hypothesized that *the children in Group III* would display poorer adjustment and poorer school results than the other groups including the controls, partly because it included a higher proportion of children with somatic and hereditary handicaps but also because the children in this group had stayed longer than other children at *infants' homes while waiting for their final placement.*

Finally I hypothesized that the children in

Table 9. *Group I adopted children. Adjustment in school compared with class controls*

Adjustment scores	Boys				Girls			
	Subjects		Controls		Subjects		Controls	
	N=90	%	N=50	%	N=73	%	N=44	%
1	26	29	28	56	45	62	33	75
2	13	15	7	14	11	15	4	9
3	31	34	9	18	9	12	5	11
4	18	20	6	12	8	11	2	5
5	2	2	0	0	0	0	0	0
Total	90	100	50	100	73	100	44	100
	A		A		B		B_1	

Diff. A—A_1 $\chi^2 = 10.97$ (3 df) $p < 0.01$ (one-tailed test)
Diff. A—B $\chi^2 = 20.94$ (3 df) $p < 0.001$

receive schooling, was dropped from this group: he was living in a foster home and at times he was very difficult to manage. One of the girls was living permanently at an institution for backward children but was included here as she was able to attend a special class.

The school adjustment of all three groups is compiled in *Table 12* in order to facilitate direct comparisons. The results of a comparison between these groups may be summarized as follows:

1. The differences between the three groups in the adjustment of the boys are rather small and not significant. In all three groups roughly one boy in five was maladjusted according to the present criteria. This result, then, does not support the hypothesis that the adopted boys in Group I would be better adjusted than the boys in the other groups.

2. The girls were better adjusted on the average than the boys in Group I and II but there was no appreciable sex difference in Group III. The adopted girls in Group I were somewhat better adjusted on the average than the girls in the other groups, but the difference is not significant.

When making inter-group comparisons, however, it must be borne in mind that the children encountered different school conditions. The children in Groups I and II were mostly living in Greater Stockholm or other urban communities whereas most of those in Group III were living in rural communities or right out in the country. This means, for instance, that the children in Groups I and II may have faced higher demands in the school situation than those in Group III. There were also differences between Group I and Group II concerning residential districts and school situation, a somewhat higher proportion of the adopted children in the former group living in more well-to-do districts with owner-occupied houses, which may have placed them in a different competitive situation from the children in Group II, whose homes were fairly evenly distributed in the Greater Stockholm area. It should be added that adjustment refers here to the school situation. As already mentioned, one foster child was too retarded to attend school but would have been counted as a problem case (adjustment score 5) on account of behavioural disturbances.

Certain behavioural and other characteristics of the subjects compared with their same-sex classmates

During the first part of the interview with teachers, before the identity of the subjects had been disclosed, all the pupils in the class were rated with respect to certain readily defined characteristics. This was done in order to obtain as objective a comparison as possible between the subjects and their classmates. Briefly, the procedure was as follows. The teacher was asked how many children of the subject's sex there were in the class; this number was divided by six and the result was rounded off to give the number of children (usually 2—3) making up a sixth of the same-sex part of the class. The teacher was then asked to give the names of the corresponding number of pupils who made up the "top" and "bottom" one sixth respectively of the same sex part of the class in respect of certain behavioural or other characteristics. The interviewer then made a note of the subjects who were placed in this way by their teacher in either the top or the bottom sixth of their sex's part of the class. The subjects not identified in this way were included in the middle group, comprising two-thirds of the children according to the expected normal distribution.

The various behavioural and other characteristics were as follows:

1. Psychomotor activity: most calm—most lively
2. Ambition: greatest—least
3. Discipline: most—least
4. Conflicts with classmates: least—most
7. Status in class: highest—lowest
9. Intelligence: highest—lowest

The interviewer pointed out that the purpose was not to detect "defects" in the pupils but simply to locate their position in the class in much the same manner as when measuring their height, which is bound to result in someone being "tallest" and someone else "shortest".

The variables listed above correspond closely to behaviour and characteristics that are common in

the school situation. They are loosely defined and open to subjective elements but this does not appear to be a disadvantage in the present context. The aim, after all, is to determine whether and to what extent teachers in general experience the present type of subjects—as a group—as different from other pupils. It occasionally took some time for the teacher to select the names of extreme pupils for a variable but usually this went quite smoothly and quickly

Results

The difference between the results and expected values was tested statistically with a goodness—of—fit test. These results are presented in *Tables 13—15* The value of X^2 denotes the magnitude of the difference between the actual and the expected distribution of the behaviour or the characteristic in question. Differences that are significant have been marked accordingly The distributions obtained in this way for a particular variable were compared with the expected distribution (1/6—2/3—1/6) These comparisons showed that the subjects in all three groups were usually over represented in the "bottom sixth of the class and under represented in the "top sixth but there were certain differences between the groups.

Group I Adopted children

The *boys* featured significantly more often than their classmates among the most lively and most conflict prone in the class. Their status in the class was also lower than expected but this difference is not significant.

The *girls* on the other hand, did not differ so markedly from their classmates. They were somewhat more conflict prone but the difference is not significant.

With respect to intelligence, on the other hand, neither the boys nor the girls deviated from the expected distribution.

Group II Childr n with their mother

The *boys* in this group differed significantly from their classmates with respect to psychomotor activity The teachers also named them more frequently as being less disciplined, less ambitious and more conflict prone than their classmates. There were no substantial differences, on the other hand, in the case of intelligence and status in class.

The *girls* in this group tended to be more lively than their classmates but did not differ markedly in other respects.

Group III Other adopted and foster children

The differences between these children and their classmates are more pronounced than in the other groups and it will be seen that the distributions for all the variables are displayed in a negative direction for the girls as well as for the boys. Unlike the case in Groups I and II, both the boys and the girls in Group III were also judged to be less intelligent than their classmates, the difference being significant for the boys ($p < 0.05$) as well as for the girls ($p < 0.01$)

Comments

These comparisons between the subjects and all their classmates complement those already presented between the subjects and their controls, which showed that the subjects were more prone than the controls to display problems in the school situation. The boys in Groups I and II were considered to be more divergent than the girls but in Group III both sexes differed to about the same degree. In all three groups there was an over representation in the "bottom sixth and an under representation in the "upper sixth of the class but seldom vice versa. It is thus clear that the teachers experienced the groups of subjects as deviating to varying degrees in a negative direction. Group I and Group II do not appear to differ much from one another whereas the deviations in Group III were still more pronounced than in the other groups.

School placement

Most of the children in the three groups were attending normal classes in the comprehensive school but a few had been placed in some form of special class. As the number of special classes arranged in a school district varies between different

Table 13 *Observed and expected distribution of behavioural characteristics Group I adopted children.*

Fraction of class	Distribution, boys Observed	Expected	Distribution, girls Observed	Expected
1 Psychomotor activity				
Upper 1/6th	7	15	14	12.2
Middle 2/3rds	52	60	46	48.6
Lower 1/6th	31	15	13	12.2
Total	90	90	73	73.0
	$X^2=22.40$ (2 df) $p<0.01$		$X^2=0.4$ (2 df)	
2. Discipline				
Upper 1/6th	13	15	16	12.2
Middle 2/3rds	56	60	43	48.6
Lower 1/6th	21	15	14	12.2
Total	90	90	73	73.0
	$X^2=2.93$ (2 df)		$X^2=2.09$ (2 df)	
3 Ambition				
Upper 1/6th	14	15	17	12.2
Middle 2/3rds	59	60	48	48.6
Lower 1/6th	17	15	8	12.2
Total	90	90	73	73.0
	$X^2=0.35$ (2 df)		$X^2=3.34$ (2 df)	
4 Conflict prone classmates				
Upper 1/6th	11	15	5	12.2
Middle 2/3rds	54	60	52	48.6
Lower 1/6th	25	15	16	12.2
Total	90	90	73	73.0
	$X^2=8.33$ (2 df) $p<0.05$		$X^2=5.67$ (2 df)	
5 Status in class				
Upper 1/6th	11	15	11	12.2
Middle 2/3rds	56	60	49	48.6
Lower 1/6th	23	15	13	12.2
Total	90	90	73	73.0
	$X^2=5.60$ (2 df)		$X^2=0.17$ (2 df)	
6 Intelligence				
Upper 1/6th	15	15	8	12.2
Middle 2/3rds	60	60	55	48.6
Lower 1/6th	15	15	10	12.2
Total	90	90	73	73.0
	$X^2=0.0$ (2 df)		$X^2=2.68$ (2 df)	

Table 14. *Obser ed and expected distribution f beha ion al characteristi s Group II, hild with biological mother*

Fraction of class	Distribution, boys Observed	Expected	Distribution, girls Observed	Expected
1 Psychomotor acti ity				
Upper 1/6th	11	17.6	9	16.2
Middle 2/3rds	57	70.8	60	64.6
Lower 1/6th	38	17.6	28	16.2
Total	106	106.0	97	97.0
		$X^2=28.81$ (2 df) $p<0.001$		$X^2=12.12$ (2 df) $p<0.01$
2 Discipli				
Upper 1/6th	7	17.6	9	16.2
Middle 2/3rds	68	70.8	76	64.6
Lower 1/6th	31	17.6	12	16.2
Total	106	106.0	97	97.0
		$X^2=16.70$ (2 df) $p<0.001$		$X^2=5.55$ (2 df) $p<0.1$
3 Ambition				
Upper 1/6th	15	17.6	14	16.2
Middle 2/3rds	66	70.8	76	64.6
Lower 1/6th	25	17.6	7	16.2
Total	106	106.0	97	97.0
		$X^2=3.82$ (2 df)		$X^2=7.54$ (2 df) $p<0.05$
4 Conflict pro classmates				
Upper 1/6th	8	17.6	5	16.2
Middle 2/3rds	76	70.8	74	64.6
Lower 1/6th	22	17.6	18	16.2
Total	106	106.0	97	97.0
		$X^2=6.72$ (2 df) $p<0.05$		$X^2=9.31$ (2 df) $p<0.01$
5 Status less				
Upper 1/6th	14	17.6	14	16.2
Middle 2/3rds	71	70.8	66	64.6
Lower 1/6th	21	17.6	17	16.2
Total	106	106.0	97	97.0
		$X^2=1.39$ (2 df)		$X^2=0.37$ (2 df)
6 Intelligenc				
Upper 1/6th	18	17.6	12	16.2
Middle 2/3rds	68	70.8	66	64.6
Lower 1/6th	20	17.6	19	16.2
Total	106	106.0	97	97.0
		$X^2=0.45$ (2 df)		$X^2=1.60$ (2 df)

Table 15 *Ob rs d and expected distribution of behavioural barat ristics Group III other adopted and foster held en.*

Fraction of class	Distribution, boys Observed	Expected	Distribution, girls Observed	Expected
1 Psychomotor activity				
Upper 1/6th	7	11.4	4	9 1
Middle 2/3rds	37	45.2	35	36 8
Lower 1/6th	24	11.4	16	9 1
Total	68	68 0	55	55.0
	X^2=17 11 (2 df) p <0 001		X^2=8.18 (2 df) p <0.05	
2. Di cipline				
Upper 1/6th	7	11.4	3	9.1
Middle 2/3rds	38	45.2	35	36.8
Lower 1/6th	23	11 4	17	9 1
Total	68	68 0	55	55.0
	X^2=14 65 (2 df) p <0.001		X^2= 11.04 (2 df) p <0.01	
3. Ambition				
Upper 1/6th	6	11.4	7	9 1
Middle 2/3rds	44	45.2	36	36 8
Lower 1/6th	18	11 4	12	9 1
Total	68	68 0	55	55.0
	X^2=6 41 (2 df) p <0 05		X^2=1.43 (2 df)	
4. Conflict prone lassmates				
Upper 1/6th	3	11 4	4	9 1
Middle 2/3rds	44	45 2	38	36 8
Lower 1/6th	21	11 4	13	9 1
Total	68	68 0	55	55.0
	X^2= 14 31 (2 df) p <0.001		X^2=4 57 (2 df)	
5 Status class				
Upper 1/6th	8	11.4	7	9 1
Middle 2/3rds	43	45 2	37	36.8
Lower 1/6th	17	11.4	11	9 1
Total	68	68.0	55	55 0
	X^2=3 87 (2 df)		X^2=0.88 (2 df)	
6 Intelligence				
Upper 1/6th	7	11.4	7	9 1
Middle 2/3rds	41	45.2	30	36.8
Lower 1/6th	20	11 4	18	9 1
Total	68	68 0	55	55 0
	X^2=8.58 (2 df) p <0 05		X^2=10.45 (2 df) p <0 01	

parts of Sweden, comparisons in this respect may be misleading and give an incorrect picture of how many pupils actually needed to attend a special class. Cities and large towns tend to have the highest proportion of special classes, whereas relatively few can be arranged in school districts out in the country and in smaller communities. In the City of Stockholm, official statistics from 1968 indicate that the incidence of pupils attending special classes was about 6 % (Holm, 1968) and the figure is probably somewhat lower in smaller communities.

Attendance at some form of special class was noted for 5.6 % of the children in Group I, 8.7 % in Group II and 7.3 % in Group III. The incidence in Group I is thus in line with the official figure for the City of Stockholm. These children, as already mentioned, were mostly living in Greater Stockholm or in towns and larger communities with a high proportion of special classes. Most of the children in Group II were also living in Greater Stockholm, so that the proportion attending special classes is somewhat higher than expected here. The children in Group III were mostly living in rural districts, many in small communities without special classes. Consequently the proportion of these children in special classes appears to have been higher than normal.

The distribution of the children between the different types of class is presented in *Table 16* from which it will be seen that 21 children (4.3 %) were in assistance classes and 21 (3.3 %) in reading classes. Four children were in hearing classes on account of severely impaired hearing.

School marks

The data obtained on school marks referred in most cases (76 %) to the spring term of the children's third school year; a few referred to the second year and the remainder to the fourth and fifth years. The lists of class marks also provided information on the subject's class control of the same sex. Only the average of the children's marks in Swedish and in Mathematics will be considered here. The calculation of significance was performed with a *t* test (one tailed).

Results

In all the comparisons with the control groups, the subject groups had the lower average mark. The results are summarized in *Tables 17—19*. In *Swedish*, however, the difference was significant only between the boys in Group III and their controls ($p < 0.05$). In *Mathematics* the difference between the adopted girls in Group I and their controls is significant ($p < 0.05$) as are the differences between the boys as well as the girls in Group III and their controls ($p < 0.001$). The girls in the various groups generally had a higher average mark than the boys (for intra-group comparisons), the differences being more pronounced in Swedish (significant in all three groups, $p < 0.01$) than in Mathematics.

Inter-group comparisons showed that the children (boys as well as girls) in Group I had a somewhat higher average mark than those in Group II in *Swedish*, the children in Group III having the lowest average mark. In *Mathematics*, on the other hand, the differences were very small between

Table 16. *Distribution by groups and sex between normal and special types of school class*

Type of class	Group I Boys	Group I Girls	Group II Boys	Group II Girls	Group III Boys	Group III Girls	Total series Boys + Girls
Normal class	84	70	91	88	65	50	448
Reading class	4	1	8	2	1	0	16
Assistance class	2	1	5	7	2	4	21
Sight, hearing or handicap classes	0	1	2	1	0	0	4
Observation class	0	0	1	0	1	1	3
Total	90	73	107	98	69	55	492

Table 17 *Mean mark in Swedish Subject Group I—III in relation to their controls.*

Marks in Swedish	Group I Adopted ch. Boys	Group I Adopted ch. Girls	Group II With biol. mother Boys	Group II With biol. mother Girls	Group III Other adopt. & foster ch. Boys	Group III Other adopt. & foster ch. Girls
Subjects						
$\bar{X}$	3.04	3.44	2.79	3.16	2.60	3.02
N	90	72	106	98	70	56
σ^2	1.0316	0.7291	0.9659	0.6946	0.6782	0.8904
	A	B	C	D	E	F
Control						
$\bar{X}$	3.16	3.54	2.96	3.18	2.97	3.09
N	90	70	106	97	68	55
σ^2	0.8742	0.7733	1.0270	0.9166	0.9841	0.6397
	A_1	B_1	C_1	D_1	E_1	F_1

	t	p <
Diff. A—B	—2.68	0.01
Diff. C—D	—2.90	0.01
Diff. E—F	—2.67	0.01
Diff. A—C	1.75	
Diff. A—E	2.96	0.01
Diff. B—D	2.15	0.05
Diff. B—F	2.65	0.01
Diff. A—A_1	—0.85	
Diff. B—B_1	—0.69	
Diff. C—C_1	—1.24	
Diff. D—D_1	—0.16	
Diff. E—E_1	—2.59	0.05
Diff. F—F_1	—0.42	

	t	p <
Diff. A_1—B_1	—2.62	0.01
Diff. C_1—D_1	—1.59	
Diff. E_1—F_1	—0.73	
Diff. A_1—C_1	1.43	
Diff. A_1—E_1	1.23	
Diff. B_1—D_1	2.49	0.05
Diff. B_1—F_1	2.97	0.01

Groups I and II while the children in Group III had significantly lower averages than those in either of the other two groups.

The sex differences were also displayed by the controls, the girls being better in general than the boys in Swedish and the sex difference in Mathematics being less marked. The controls for Group I had higher average marks than the controls for the other two groups. This indicates that the adopted children in Group I were generally subjected to greater competition and had a higher proportion of intelligent and/or receptive classmates than the children in the other groups.

It would obviously be wrong to draw far reaching conclusions about the children's intelligence or ability on the basis of their school marks, which constitute a relatively uncertain measure in this respect. It is nevertheless clear that the children in Group III had difficulty in matching the marks of their classmates as well as those of the subjects in the other two groups. Their inferior average result also reflects the inferior potential of these children in the class comparisons, as already mentioned, the teachers frequently judged children in Group III to be less intelligent than their classmates but this was by no means the case in the other two groups.

The relative frequency of children with a weak intelligence in Group III no doubt has to do with the various forms of handicap noted at an early age in a larger number of these children.

School problems and nervous disturbances according to the school health card

An entry is made on the school health card if the pupil is remitted to the school *psychiatrist*,

Table 18. *Mean marks in Mathematics. Subjects in Groups I—III in relation to their controls*

Marks in Mathematics	Group I Adopted ch. Boys	Girls	Group II With biol. mother Boys	Girls	Group III Other adopt. & foster ch. Boys	Girls
Subjects						
$\bar{X}$	2.98	3.05	2.99	2.98	2.59	2.65
N	90	72	106	98	70	56
σ^2	1.0781	0.7515	1.2475	0.7623	0.7677	0.7839
	A	B	C	D	E	F
Control						
$\bar{X}$	3.24	3.41	3.12	3.07	3.16	3.13
N	90	70	106	97	68	55
σ^2	1.1979	0.9706	1.1751	0.7758	1.0627	1.0760
	A_1	B_1	C_1	D_1	E_1	F_1

	t	p <
Diff A—B	—0.33	
Diff C—D	0.07	
Diff E—F	—0.25	
Diff A—C	—0.06	
Diff A—E	2.53	0.05
Diff B—D	0.37	
Diff B—F	2.59	0.05
Diff. A—A_1	—1.64	
Diff B—B_1	—2.47	0.05
Diff C—C_1	—0.86	
Diff D—D_1	—0.72	
Diff E—E_1	—3.52	0.001
Diff F—F_1	—2.74	0.01

	t	p <
Diff A_1—B_1	—1.02	
Diff C_1—D_1	0.36	
Diff E_1—F_1	0.16	
Diff A_1—C_1	0.77	
Diff A_1—E_1	0.47	
Diff. B_1—D_1	2.14	0.05
Diff B_1—F_1	1.53	

Table 19. *Mean marks in Swedish and in Mathematics. All boys and all girls in relation to their controls*

	Boys Subjects	Controls	Girls Subjects	Controls
Swedish				
$\bar{X}$	2.85	3.03	3.22	3.27
N	266	264	226	222
σ^2	0.9339	0.9647	0.7749	0.8516
	A	A_1	B	B_1
Mathematics				
$\bar{X}$	2.88	3.17	2.91	3.42
N	266	264	226	222
σ^2	1.0872	1.1481	0.7777	0.5699
	C	C	D	D_1

Swedish	t	p <
Diff. A—A_1	—2.39	0.05
Diff. B—B_1	—0.39	
Diff. A—B	—4.70	0.001
Diff A_1—B_1	—2.79	0.01

Mathematics	t	p <
Diff C—C_1	—3.20	0.01
Diff D—D_1	—6.59	0.001
Diff C—D	—0.34	
Diff C_1—D_1	—2.95	0.01

Table 20. *School problems and nervous disturbances recorded on school health cards Group I—III (N=497*)*

	Group I		Group II		Group III	
	Boys	Girls	Boys	Girls	Boys	Girls
1. Remitted to school psychiatrist or child guidance clinic						
Yes	10	2	24	13	4	6
No	81	71	84	86	65	51
Total	91	73	108	99	69	57
2. Pedagogic and psychological analysis						
Yes	13	1	40	23	8	12
No	78	72	68	76	61	45
Total	91	73	108	99	69	57
3. Nervous disturbances or other problems						
Yes	30	6	40	26	8	8
No	61	67	68	73	61	49
Total	91	73	108	99	69	57
4. Problems and disturbances under one or more of alt. 1—3						
Yes	35	6	49	32	12	14
No	56	67	59	67	57	43
Total	91	73	108	99	69	57

* Incl. the 5 subjects not covered by the interviews with teachers.

department for child psychiatry or a child guidance clinic, or if the pupil has been the subject of a pedagogic and psychological analysis or displayed nervous symptoms or some other problem. These entries were noted and compiled for each group. Corresponding information was not, however available for the controls and nor could any exact estimate be obtained of the frequency with which pedagogic and psychological analyses or consultations with child psychiatrists occur in a representative school population. It has been reported, however that in schools in Stockholm the proportion of pupils remitted to school psychiatrists is 3 % in classes 1—3 and 1.7 % in classes 4—6 and that approximately two-thirds of those remitted are boys (Hedqvist, 1969).

It will be seen from *Table 20* that school problems were relatively common in all three groups and most common in Group II (children living with their mother). The frequency is no doubt considerably higher than one would expect in a "normal" population. When making inter group comparisons however, it must be remembered that the children in Group III probably had less access to psychiatric, psychological and pedagogic services than those in the other two groups since so many of them lived in rural communities where such services are less well developed.

The analysis of school health cards also showed that quite a number of the children in Group II but none of the adopted children in Group I were judged to have been *neglected*. We have already seen that school adjustment and school results in Group II were relatively good compared with Group I but the interviews with teachers and the school health cards left the general impression that many of the children in Group II

were living under difficult economic and social circumstances. Nor is this surprising. Indeed, it is remarkable that, in spite of the social handicaps of many of the children in this group, not more of them were maladjusted or problem children.

ANALYSIS OF THE RESULTS

Adjustment scores related to background variables

The following analyses, undertaken in the form of cross-tabulations with X^2 tests, are intended to show whether some of the background variables reported above are associated with the children's school adjustment. The backgrund variables used are

1. Complications during pregnancy and birth
2. Institutional care during the first year of life (maternal deprivation)
3. Registered criminality and abuse of alcohol among the biological fathers

Many other factors could of course be suggested in this context but these have been chosen as being available and at the same time of theoretical and practical value. The three groups of subjects are reported separately because the different conditions under which the children have grown up may well have interacted in different ways with these backgrund factors. In the case of perinatal factors, for instance, I have assumed that the importance of any negative influence may vary depending on the childhood environment. Werner et al (1967) have shown, for instance, that perinatal complications and an inadequate social environment have a cumulative negative effect on the child's development and adjustment, whereas a favourable environment appears to neutralize the effect of perinatal stress. This reasoning may well apply to other backgrund factors as well, for instance maternal deprivation (institutional care during infancy) and criminality among the biological parents.

Registered criminality and abuse of alcohol are of course weak indicators of personal and social functioning but it has been shown (Jonsson & Kälvesten, 1964) that such records may be correlated to the adjustment of children who live with their parents, an association that has been interpreted as reflecting heredity as well as environment. The present study where many of the children have been separated from their biological parents, provides an opportunity of testing whether such an association reflects heredity or environment, or a combination of the two

Complicated pregnancy and birth related to school adjustment

All complications noted in the maternity records have been included in the following analysis regardless of their nature. It did not prove feasible to break down the subjects by different types of complication. In the analysis the subjects have been divided as a rule by sex and adjustment scores (1 2, 3 and 4—5) on the hypothesis that complications during the biological mother's pregnancy lead to poorer school adjustment in the child.

Results

Group I There is a tendency in the direction of the hypothesis for girls but the relationship is not significant *(Table 21)*

Table 21 *Complication during pregnancy related to adjustment Group I adopted children*

Complications during pregnancy	Boys Adjustment scores 1	2	3	4+5	Total	Girls Adjustment scores 1	2	3	4+5	Total
Yes	8	3	11	6	28	13	2	4	4	23
No	18	10	20	14	62	32	9	5	4	50
Total	*26*	*13*	*31*	*20*	*90*	*45*	*11*	*9*	*8*	*73*
	X^2=0 44 (2 df)					X^2=2.48 (1 df) with scores 3 and 4+5 combined.				

Table 22. *Complications during pregnancy related to adjustment in Group II children with biological mother*

Complications during pregnancy	Adjustment scores Boys					Adjustment scores Girls				
	1	2	3	4+5	Total	1	2	3	4+5	Total
Yes	15	9	6	9	39	17	4	13	1	35
No	18	16	21	11	66	32	11	10	8	61
Total	33	5	27	20	105	49	15	3	9	96

$X^2=4.09$ (3 df) $X^2=1.42$ (2 df)

Group II No tendency was observed in the expected direction *(Table 22)*

Group III There is a weak correlation between the boys adjustment scores and complications during pregnancy significant at the 0.05 level (one-tailed test) There is also a similar but non-significant correlation for the girls *(Table 23)*

Complications during pregnancy were probably of secondary importance for the children's adjustment scores but as the number of observations in each group is small, it is difficult to draw definite conclusions. For the three groups combined, however there is a definite tendency in the expected direction for girls, the correlation being significant at the 0.05 level (one-tailed test, *Table 24)* but no such correlation was found for the boys. Birth complications did not show any co-variation with the children's adjustment in the three groups and for this reason tables are omitted.

Maternal deprivation

The concept of maternal deprivation and its importance for the development of personality was the subject of lively debate during the Fifties, initiated for instance by the studies of children at institutions undertaken by Goldfarb (1943) Spitz (1945) and Spitz & Wolff (1946) In *Maternal Care and Mental Health* (1951) Bowlby was pessimistic about the effects of institutional care and maternal deprivation during the first years of life but this view was subsequently modified by him (Bowlby et al., 1956) and other authors (Ainsworth, 196.) Some writers, however still consider that early loss of maternal contact involves a grave danger of upsetting the development of personality Asociality criminality or "the disease of non-attachment (Fraiberg, 1968) have thus been associated with maternal deprivation. This point of view has been put forward mainly by the psychoanalytical school, whereas sociologists have been more sceptical about the importance of maternal deprivation, particularly in relation to asociality or criminality Barbara Wootton (1959) for instance, writes as follows in *Social Science and Social Pathology* "That damage is lifelong or irreversible, that maternal deprivation is a major factor in criminal behaviour or that the younger the child the greater the risk, all these must be regarded as quite unproven hypotheses Several studies suggest in fact that most people are able to compensate even for severe deprivation at an early age (Skeels, 1965

Table 23 *Complications during pregnancy related to adjustment in Group III other adopted and foster children*

Complications during pregnancy	Boys Adjustment scores					Girls Adjustment scores				
	1	2	3	4+5	Total	1	2	3	4+5	Total
Yes	7	2	10	5	24	11	4	3	6	24
No	19	10	6	10	45	18	6	2	5	31
Total	26	12	16	15	69	29	10	5	11	55

$X^2=4.92$ (2 df) $X^2=1.47$ (2 df)
$p < 0.05$ (one-tailed test)

Table 24 *Complicat on during pr gnancy lated to adjustment Groups I—III combined*

Complications during pregnancy	Boys Adjustment scores					Girls Adjustment scores				
	1	2	3	4+5	Total	1	2	3	4+5	Tot
Yes	30	14	27	20	91	41	10	20	11	82
No	55	36	47	35	173	82	26	17	17	142
Total	85	50	74	55	264	123	36	37	28	224
	$X^2=1.17$ (3 df)					$X^2=6.72$ (3 df) $p<0.05$ (one-taile test)				

Kadushin 1966, Heston & Denney 1968) The debate seems to have suffered from the synonymous use of the terms maternal separation and "deprivation as well as by a lack of precision in the use of the term "deprivation" (Yarrow 1965) Sociological researchers have also criticized the tendency of "separationists to argue from relatively small clinical populations without allowing for genetic or other selective factors (Clarke, 1968 Rosenthal, 1970) Insufficient allowance has been paid in the past to the prevalence of different forms of deprivation in the population at large and Wootton (op.cit.) calls for demographic studies to clarify this aspect. It has been reported by Munro (1965) that interviews with a non psychiatric series of 210 out patients showed that approximately 20 % had lost one or both parents before their sixteenth birthday Furthermore 32 % reported that they had been separated from one or both parents for some other reason than death for at least three months as a child. Taking all the reasons for separation together 46 7 % had been subjected to parental bereavement durin childhood A disturbed relationship with one o both parents during childhood was reported b 18 % The report does not state, howeve whether "bereavement occurred during infancy I must nevertheless be concluded that parental be reavement is comparatively common among non psychiatric patients.

The following analysis is intended to show whether the time spent at an infants home bear any relationship to the children s adjustment. Th purpose is thus to test whether maternal depriva tion and institutional care for different length of time has any connection with the children adjustment.

The duration of institutional care is determined by numerous factors, as discussed in detail in my earlier study (Bohman, 1970) Here it will suffice to note that it seems reasonable to suppose that a number of children spent a relatively long time at infants homes just because they were difficult to place on account of premature birth, postnatal

Table 25 *Infants' hom stay or no stay elated to adjustment Group I—III mbined*

Stay at infants home	Boys Adjustment scores				Girls Adjustment scores			
	1+2	3	4+5	Total	1+2	3	4+5	Total
Yes	91	56	39	186	108	22	19	149
No	43	19	17	79	51	17	9	77
Total	134	75	56	265	159	39	28	226
	X =1 06 (2 df)				$X^2=1.90$ (2 df)			

Table 26. Infants' home duration of stay related to adjustment. Group I adopted children

Duration of stay in months	Boys Adjustment scores				Girls Adjustment scores			
	1+2	3	4+5	Total	1+2	3	4+5	Total
0	1	1	1	3	2	0	1	3
0—2	3	3	0	6	8	0	0	8
3—5	19	9	10	38	25	7	1	33
6—8	14	13	8	35	15	1	5	21
9—11	2	4	1	7	6	1	1	8
12—14	0	1	0	1	0	0	0	0
Total	39	31	20	90	56	9	8	73
	$X^2=2.19$ (2 df)				$X^2=0.50$ (1 df)			

complications or developmental disturbances that were detected at an early stage. Such complications may naturally co-vary with subsequent difficulties in adjustment and need not have any direct connection with the time during which the child was deprived of a continuous maternal contact.

The tables of results include the children who, instead of being sent to an infants' home, were placed directly from the maternity clinic, usually with the biological mother. The time spent at an infants' home has been divided into three-monthly intervals in the tables and the children with adjustment scores 1 and 2 have been combined as have those with scores 4 and 5.

Results

No difference in adjustment was found between the children who stayed at an infants' home and those who did not *(Table 25)*. When the analysis is confined to those who did receive institutional care, however, there is a clear over-representation of girls with adjustment scores 4—5 among those who stayed at institutions for more than six months. It will be seen from *Tables 26—28* that this tendency is apparent in all three groups and is significant ($p<0.01$) for the total series *(Table 29)* dichotomized into stay of more and less than six months. One then finds that of the 19 girls who were judged to be maladjusted (scores 4—5) in school, 17 (89 %) had spent more than six months at an infants' home compared with only 63 (58 %) of the 108 girls with scores 1—2. No such correlation was found for the boys.

Discussion

There is thus support for the hypothesis that the duration of institutional care is related to subsequent adjustment, though only for the girls in this

Table 27. Infants' home duration of stay related to adjustment. Group II children with biological mother

Duration of stay in months	Boys Adjustment scores				Girls Adjustment scores			
	1+2	3	4+5	Total	1+2	3	4+5	Total
0	32	15	14	61	45	17	6	68
0—2	6	0	2	8	3	2	0	5
3—5	5	4	2	11	3	1	0	4
6—8	8	2	2	12	8	1	3	12
9—11	6	2	1	9	4	2	0	6
12—14	1	5	0	6	1	2	0	3
Total	58	28	21	107	64	25	9	98
	$X^2=2.25$ (4 df)				$X^2=0.07$ (1 df)			

Table 28. *Infants' home duration of stay related to adjustment Group III other adopted and foster children*

Duration of stay in months	Boys Adjustment scores				Girls Adjustment scores			
	1+2	3	4+5	Total	1+2	3	4+5	Total
0	10	3	2	15	4	0	2	6
0— 2	3	0	1	4	2	1	0	3
3— 5	3	1	3	7	4	1	1	6
6— 8	3	4	0	7	6	0	2	8
9—11	12	5	3	20	16		3	17
12—14	6	3	6	15	7	1	3	11
Total	37	16	15	68	39	5	11	55

$X^2=3.76$ (3 df) $X^2=0.59$ (2 df)

study. The question then arises whether this is a causal connection that is an expression for maternal deprivation due to the children's institutional care, or whether it reflects selective factors, such as premature birth and complications during pregnancy or birth, which could be correlated to the children's adjustment as well as to the duration of institutional care. It was found, however that these complications did not affect the correlation between institutional care and adjustment scores for the girls *(Table 30)*

Other selective factors may of course have been involved and contributed to the correlation observed but one would expect them to have affected boys and girls in a similar manner and resulted in a correlation between the boys' adjustment and institutional care as well. For the moment it must be accepted that there is support for the hypothesis that the duration of institutional care is related to the girls' adjustment scores. The lack of such a relation in the case of the boys could conceivably express a constitutional difference between the sexes, manifested in this case in the girls being more sensitive to early maternal and/or social deprivation.

The social heredity"; The importance of criminality and abuse of alcohol in the biological background

There are still those who hold that social maladjustment among children as well as adults can be inherited, by which is meant that, for instance, alcoholism, criminality or asociality may be determined biologically and genetically. This opinion has been questioned, criticized and rejected in a whole series of studies which instead have emphasized the importance of the environment for the development of the personality. In studies of adoptive or foster children who were separated as infants from their parents, so that hereditary and environmental factors could be controlled, no

Table 29 *Stay of less or more than 6 months at infants' home related to adjustment Group I—III combined*

Duration of stay in months	Boys Adjustment scores				Girls Adjustment scores			
	1+2	3	4+5	Total	1+2	3	4+5	Total
0— 5	39	17	18	74	45	12	2	59
6—14	52	39	21	112	63	10	17	90
Total	91	56	39	186	108	22	19	149

$X^2=3.10$ (2 df) $X^2=8.96$ (2 df) $p < 0.01$ (one-tailed test)

correlation was found between alcoholism in the biological background and occurrence of alcoholism in children as adults (Roe & Burks, 1945). Nor did my earlier study of adopted children (Bohman, 1970) reveal any correlation between their adjustment and the incidence of registered criminality or abuse of alcohol among their biological parents. Since the lack of a correlation applied to both sexes, they were reported together (op.cit. p. 176).

In the case of children or adults whose maladjustment is severe, however, several writers have argued that genetic as well as environmental factors may be involved (Otterström, 1946, Cowie et al., 1968). This opinion seems to be shared by Jonsson (1967) in his study of delinquent boys, while Lee Robins (1966), who followed children up to adulthood from a child guidance clinic, concluded that genetic factors are of decisive importance for the genesis of a so-called sociopathic personality. Similar results have been reported by Schulsinger (1971) on the basis of large series of adopted persons and their relatives.

We have already seen that registered criminality and abuse of alcohol were considerably over-represented among the biological parents, particularly in Group III (p. 9). The lack of detailed information concerning the biological background prevents any further assessment of how the biological parents function as adults, but the large incidence of biological fathers with entries in these registers suggests that, compared with the population at large, an unusually high proportion had difficulty in coping with their social relationships. This is also indicated by the circumstance that most of the fathers in question had three or more entries in these registers and that criminality and abuse of alcohol commonly went hand in hand. What this in turn was due to is impossible to tell, but it can be presumed as a hypothesis—in keeping with the opinions and theories outlined above—that the biological parents constitute a negative genetic selection, manifested in a high proportion of deviant personalities with social problems. Working on this hypothesis it would also be reasonable to assume that the children of biological parents who display social maladjustment are also likely to manifest more behavioural disturbances than other children irrespective of whether or not they grow up together with these parents.

The data were analyzed on the basis of these hypotheses and the results are presented in *Tables 31—40*. The analysis had to be confined to registered criminality and abuse of alcohol among the biological fathers because, as already mentioned, the biological mothers occurred too seldom in the registers to permit a statistical analysis.

The following circumstances should be borne in mind when considering the results. The adopted children in Group I were entirely separated from their biological environment from birth and were therefore entirely excluded from any social influence from that quarter. The children in Group II had grown up with their biological mother; a small proportion of these children lived with both their biological parents but most of them appear to have had no or only very early contact with their biological fathers. In Group III, finally, the

Table 30. Stay of less or more than 6 months at infant homes related to adjustment. Group I—III combined, with all cases of complications during pregnancy and birth and all premature births excluded.

Duration of stay in months	Boys Adjustment scores				Girls Adjustment scores			
	1+2	3	4+5	Total	1+2	3	4+5	Total
0—5	30	8	12	50	30	6	1	37
6—14	30	20	9	59	33	5	8	46
Total	60	28	21	109	63	11	9	83
	$X^2=4.85$ (2 df)				$X^2=4.73$ (2 df) $p<0.05$ (one-tailed test)			

able 31 *Criminality among kno biological fath elated to adj stment Group I ad pted hild n.*

ntry in Criminal Register	Boys Adjustment scores			Girls Adjustment scores		
	1+2	3	4+5	1+2	3	4+5
es	12	7	5	12	2	2
o	23	21	13	37	6	6
otal	35	28	18	49	8	8
	$X^2=0.31$ (scores 3, 4+5 combined)			$X^2=0.09$ (scores 3, 4+5 combined)		

Table 33. *Criminality among kno biological fathers related to adjustment in Group III other adopted and f ster hild en*

Entry in Criminal Register	Boys Adjustment scores			Girls Adjustment scores		
	1+2	3	4+5	1+2	3	4+5
Yes	17	4	3	11	3	4
No	15	8	11	22	2	5
Total	32	12	14	33	5	9
	$X^2=4.06$ $p<0.05$ (scores 3, 4+5 combined)			$X^2=1.16$ (scores 3, 4+5 combined)		

reat majority of the children had no contact with heir biological parents from infancy The children n Groups II and III seem to have had a more d erse and insecure childhood on the average han those in Group I.

The *results* of the correlation analyses concerning riminality can be summarized as follows

In *Group I* there was no correlation between he registered background factors and the adjust nent of either the girls or the boys *(Table 31)*

In *Group II* there was no such correlation for he boys but disturbances and maladjustment were ignificantly more frequent among the girls whose ather appeared in the Criminal Register ($p<0.05$ *able 32)*

In Group III a relationship was found similar o that in Group II, girls whose father appeared n the Criminal Register displayed more distur ances than other girls the correlation, however was weak and not significant. The relationship for the boys was the opposite of that expected boys whose father appeared in the Criminal Register had lower adjustment scores than other boys *(Table 33)*

The results are thus contradictory and difficult to interpret It is clear that the adjustment of the adopted children in Group I and of the boys in Groups II and III was not associated with registered criminality but this may have been important for the girls in Groups II and III The correlation is admittedly weak and not statistically significant in Group III If the girls in Groups II and III are combined and the breakdown by adjustment scores is dichotomized into scores 1—2 and 3—5 the correlation between the fathers criminality and the girls adjustment becomes clearer and is definitely significant ($X^2 = 4.30$ $p<0.05$ *Table 34)* A similar analysis of adjust ment in relation to registered criminality shows a significant sex difference in Groups II and III

Table 32 *Criminality among kno biological father elated to adjustment in Group II, children ith biological mother*

ntry in Criminal Register	Boys Adjustment scores			Girls Adjustment scores		
	1+2	3	4+5	1+2	3	4+5
es	13	7	5	21	11	6
o	37	20	14	37	10	2
otal	50	27	19	58	21	8
	$X^2=0.427$ (scores 3 4+5 combined)			$X^2=3.984$ $p<0.05$ (scores 3, 4+5 combined)		

Table 34. *Criminality among kno biological father* related to adjustment Groups II and III combined.

Entry in Criminal Register	Boys Adjustment scores			Girls Adjustment scores		
	1+2	3	4+5	1+2	3	4+5
Yes	30	11	8	32	14	10
No	54	28	25	59	12	7
Total	84	39	33	91	26	17
	$X^2=1.16$ (scores 3, 4+5 combined)			$X^2=4.30$ $p<0.05$ (scores 3, 4+5 combined)		

Table 35. *Boys and girls in Group II and III with adjustment scores 3—5 related to registered criminality among biological fathers.*

Entry in Criminal Register	Boys (scores 3—5) N	%	Girls (scores 3—5) N	%
Yes	19	6	24	56
No	55	74	19	44
Total	7	100	43	100

$X^2 = 8.74$ $p < 0.01$

($p < 0.01$ *Table 35*). Of all the boys with an adjustment score of 3—5 only about a quarter had a father with a criminal record compared with more than half of the girls with this degree of maladjustment. The results thus speak for a criminal background as a contributory cause of the maladjustment in the girls but not in the boys.

Much the same tendencies as for registered criminality were obtained when the children's adjustment scores were cross tabulated with registered *abuse of alcohol* (see *Tables 36—38*). The adopted children in Group I thus showed no association at all between these variables. In Groups II and III the girls' adjustment scores covaried with the independent variable and a clearer though not a significant relationship was obtained when the two groups were combined (*Table 39*). It will be seen from *Table 40* that 51 % of the fathers of girls with symptom loads of 3—5 had been registered for offences under the Temperance Act compared with only 36 % of the boys' fathers, though this difference is not significant.

Discussion

The correlation between criminality among the biological fathers and the adjustment scores of their daughters thus supports the hypothesis that social maladjustment, nervous symptoms and behavioural disturbances may be determined genetically. The results are somewhat contradictory however since similar relationship were not found either between the boys and their fathers in any of the groups or for the girls in Group I. Before accepting a genetic cause for this relationship, however one must rule out the possibility of contamination between hereditary and environmental factors, for instance through persons in the child's surroundings knowing about the biological father's criminal record. Negative expectations arising from such knowledge could create an unfavour

Table 36. *Abuse of alcohol among the biological fathers related to adjustment. Group I adopted children*

Offence under Temperance Act	Boys Adjustment scores 1+2	3	4+5	Girls Adjustment scores 1+2	3	4+5
Yes	8	8	4	14	4	0
No	27	20	14	35	4	8
Total	35	28	18	49	8	8
	$X^2 = 0.005$ (scores 3, 4+5 combined)			$X^2 = 0.002$ (scores 3, 4+5 combined)		

Table 37. *Abuse of alcohol among biological fathers related to adjustment. Group II children living with their biological mother*

Offence under Temperance Act	Boys Adjustment scores 1+2	3	4+5	Girls Adjustment scores 1+2	3	4+5
Yes	17	10	6	4	10	4
No	33	17	13	34	11	4
Total	50	7	19	38	1	8
	$X^2 = 0.018$ (scores 3, 4+5 combined)			$X^2 = 0.013$ (scores 3, 4+5 combined)		

Table 38. *Abuse of alcohol among the biological fathers related to adjustment. Group III other adopted and foster children*

Offence under Temperance Act	Boys Adjustment scores 1+2	3	4+5	Girls Adjustment scores 1+2	3	4+5
Yes	20	5	5	12	4	4
No	12	7	9	21	1	5
Total	32	12	14	33	5	9
	$X^2 = 2.20$ (scores 3, 4+5 combined)			$X^2 = 0.99$ (scores 3, 4+5 combined)		

Table 39. *Abuse of alcohol among the biological fathers related to adjustment. Groups II and III combined*

Offence under Temperance Act	Boys Adjustment scores			Girls Adjustment scores		
	1+2	3	4+5	1+2	3	4+5
Yes	37	15	11	36	14	8
No	45	24	22	55	12	9
Total	82	39	33	91	26	17
	$X^2=0.94$ (scores 3, 4+5 combined)			$X^2=1.16$ (scores 3, 4+5 combined)		

able climate and lead to nervous disturbances in the child. In my opinion, however, knowledge of the biological fathers can hardly have been an important negative factor in the children's environment. Had this been the case, one would expect this factor to have been equally or even more important for the adjustment of the boys whereas in fact the relationship applied only to the girls, while for the boys the tendency was, if anything, the opposite.

In Group II about 30 % of the fathers were living with the biological mother. Registered criminality among these fathers was approximately as frequent as among the other fathers in this group and the relationship between their daughters' adjustment and this criminality was also similar, which suggests that the fathers were of no importance as an "environmental factor" in this respect. In this context it is also necessary to consider the possibility of the results having been affected by so-called assortative mating. It is thus conceivable that mothers who have children with socially maladjusted men may themselves display maladjustment or mental disturbances to a greater extent than other mothers. We have already seen that criminality and abuse of alcohol were substantially over-represented among the biological mothers, especially in Group III, which suggests that various forms of maladjustment were more common in this group of women than in a normal population. Presumably therefore the mothers, like the fathers, represent a negative genetic selection so that, if genetic factors influenced the children's adjustment, some of the children were liable to inherit a "burden" from both parents. But this risk should surely be the same for boys as for girls.

Table 40. *Boys and girls in Groups II and III with adjustment scores 3—5 related to registered abuse of alcohol among biological fathers*

Offence under Temperance Act	Boys (scores 3—5) N	%	Girls (scores 3—5) N	%
Yes	26	36	22	51
No	46	64	21	49
Total	72	100	43	100

$X^2=1.93$

Thus, while there are many indications that the association between the adjustment of the fathers and their daughters is conditioned by genetic factors, one is left with the paradox that this did not apply to the boys. The clearly significant difference between the boys' and the girls' relationships to socially deviant fathers suggests to me the possibility of a constitutional difference between the dispositions of boys and girls to develop nervous symptoms and behavioural disturbances. It is of course conceivable that the difference between the sexes is an artifact of the methods employed in this study but this seems unlikely to say the least: the "symptoms" registered were the same for both sexes, in most cases "explicit" manifestations that are readily observed by those in the individual's environment, e.g. psychomotor activity, difficulty in concentrating, dyslexia, conflicts with peers and so on. Furthermore, an analysis of the teachers' more objective assessments of the children in relation to their classmates (see p. 15) gave the same trend: girls in Groups II and III whose fathers had a criminal record tended to display a negative "deviation", whereas this was seldom the case with the boys.

A possible explanation for the girls but not the boys displaying a relationship with their fathers' criminality and abuse of alcohol could be that the two sexes manifest such relationships at different ages. It is thus conceivable that such a relation

ship would be found for the boys when they are older.

The problem of male and female dispositions for different diseases is an intricate one and it is difficult to obtain a general picture from the present literature of the various theories that attempt to explain the differences that exist. It is known, however that boys are more prone than girls to display difficulties of adjustment and nervous symptoms (see e.g. Rutter 1970) and this was the case in the present study This has been interpreted as a manifestation of constitutional d fferences but also of differences n the upbring ing of the two sexes Asociality and deliquency are also considerably more common among boys than girls. At the same time, asociality among girls is much more closely associated with an adverse environment than it is among boys. In other words, more environmental stress is required to elicit maladjustment among girls (Cowie et al 1968) Rutter (op cit) has discussed the various factors that may play a part in the psychic development of boys and girls boys thus develop anti social symptoms more f equently than girls in response to conflicts within the family which may indicate that boys are more sensitive to environ mental influences than girls the presence of psy chiatric disorders among girls appears instead to be due more frequently to genetic factors (Rutter, 1970 p 184)

The findings in the present study can hardly serve as a basis for further discussion and con clusions concerning the association between biological background and children symptoms but the results do favour the hypothesis put forward by Rutter that psychiatric disorders among girls are conditioned by genetic factors more frequently than they are among boys.

This leaves the question why the adjustment of the gi ls in Group I did not display the same relationship as n the other two groups It is conceivable that the genetic load in this group was weaker than in the other two and did not produce an effect on this account. But t is also possible that these girls were living in more sheltered environments than the other girls at the time of this study and that their environment neutralized their "heritage

It goes without saying that these conclusions are purely tentative. The study was intended to be descriptive and exploratory and it was not specially designed to handle the question of heredity and environment. The findings and relationships nevertheless appear to warrant further investigations along these lines, designed explicitly to illuminate the importance of hereditary factors for different forms of social insufficiency among men as well as women.

GENERAL DISCUSSION AND SUMMARY

This study was prompted by certain questions that often arise in connection with child welfare: How do children who are placed in adoptive or foster homes develop and adjust? Is a child s development affected by the mother having been exposed to stress during pregnancy? Does institu tional care during infancy have any effect on the subsequent adjustment of the child? What is the importance of hereditary factors in the biological background for the child s development and subse quent adjustment?

The study has been based on 624 children whose mothers had applied to the Child Welfare Committee at the time of their birth to have them adopted. Most of these mothers were unmarried or living alone and wished to have their child adopted for material as well as psychological easons.

A follow up study was made when the children were 10—11 years old. It covered 492 children for whom nformation was collected concerning their school marks, school adjustment and so on. At the same time corresponding data were obtained for the children s classmates as well as for individual controls of the same sex. Further information was obtained from the maternity records, about the time spent at infants homes and about official ecords of criminality and abuse of alcohol among the biological parents.

At the time of the follow-up some of the child en were living in thei biological env ronment and others were not (i e n adopt ve or foster

homes) and the material was divided into three groups on the basis of their placement

Group I Children placed in adoptive homes through the Stockholm Adoption Agency (n = 163) These adoptive families were mostly living in Greater Stockholm or other urban regions. The parents had a higher social and economic standard than parents in general.

Group II Children in their biological environment (n = 205) These children were living with their biological mother Approximately one-third of these mothers were married to the biological father and most of the others had married someone else, so that only a small proportion were still unmarried. These families were also living in Greater Stockholm but the social and economic situation of the children was no doubt less favourable than that of the children in Group I.

Group III Other adopted and foster children (n = 124) These children were living in adoptive or foster homes, where most of them had been placed through the appropriate agency of the Child Welfare Committee. The Adoption Agency had been unable to place some of these children directly on account of somatic handicaps, retarded development or hereditary reasons. In a number of cases the mothers had not been able to reach a decision to place the child in an adoptive home and it was therefore placed in a foster home, where in some cases it was subsequently adopted. The children in this group thus constitute a negative selection. In contrast to the other two groups, most of these families were living in small communities or right out in the country

The children in the three groups were thus all in much the same position at the time of their birth but the conditions under which they grew up varied greatly on account of the different decisions that were made on their behalf One of the purposes of the study has been to make a retrospective assessment of the extent to which these decisions concerning placement resulted in differences in the development and adjustment of the children.

The adjustment of the children was classified on the basis of interviews with teachers, using a five-point scale of adjustment scores children with manifest problems at school (problem children) having a score of 4—5 The results revealed rather small differences between the boys in the three groups about one *boy* in five was classified as a problem child in every group Among the controls, on the other hand, only 8—12 % were classified as problems. Approximately 10 % of the *girls* in Group I and II but 20 % of those in Group III were problem cases compared with only about 5 % among the controls.

It is therefore clear that, irrespective of their placement, the subjects displayed nervous disturbance or difficulties of adjustment more frequently than their classmates. The adjustment of the boys did not vary with the type of placement, which is somewhat surprising as one might expect that the poorer environment of the children in Groups II and III could have resulted in a higher incidence of problem cases compared with Group I. It was only the girls in Group III who had a higher incidence of problem cases compared with the girls in the other two groups.

Comparisons between the subjects and all their classmates with respect to certain behaviour in school (e.g. psychomotor activity proneness to conflicts, status, intelligence etc.) also showed that the teachers experienced the subjects as deviating in a negative direction more often than expected. The differences were greatest for the boys in all three groups. Inter groups comparisons showed that the children in Group III had the greatest deviations. It is thus clear that children whose conception is unwelcome and whose mother contemplates having them adopted are liable to develop more nervous disturbances and symptoms of maladjustment than other children regardless of whether they grow up with their biological mother in an adoptive home or in a foster home. The subjects had a somewhat lower average mark in *Swedish* than the controls but the difference was not significant except in Groupp III. Their average marks in *Mathematics* were also somewhat lower than those of the controls, the differences being significant for the girls in Group I as well as for both sexes in Group III compared with the controls.

Inter group comparisons showed that the children in Group III had lower average marks than those in the other two groups, which is probably a sign of these children's inferior ability This in turn is no doubt connected with the circumstance that these children as already mentioned, constitute a negative selection in terms of placement. This is also indicated by the teacher's assessments of the children's intelligence.

Problem cases were thus over-represented in the present series of children and so was a poor school performance in certain groups. Only a limited analysis can be made of the causal factors underlying these findings. A priori the factors could be genetic as well as environmental But only a few factors concerning the children's biological background and childhood environment were known and available for analysis. Environmental details were known only for some of the children in Group I which means that the essential question of the children's adjustment to and relation with their family must be omitted from the discussion of etiology

Complications during pregnancy were noted in 30—40 % of the cases and were most frequent in Group III. It is probable that such complications were more common on the whole in this series compared with a representative group of mothers. Complications during pregnancy were significantly related to adjustment among the girls in the series as a whole but not when each group was analyzed separately In Group III, however, the adjustment of the boys was significantly associated to such complications and a similar but non-significant association was found for the girls. The results thus point to a weak correlation between dependent and independent variables, suggesting that complications during pregnancy provide some but not a major explanation for the chilren's adjustment scores. This finding is of some interest in principle because it tends to show that difficulties of adjustment among children may be connected with stress during pregnancy Similar findings have been reported from other studies (Pasamanick et al, 1956, Werner et al, 1967 Stott, 1969) Birth complications, however did not show any correlation with the children later adjustment

Institutional care Approximately two-thirds of the children had spent various lengths of time at an infant's home, being placed there as a rule from the maternity clinic. The general standard and staff at these homes appear to have been good, though there were certain differences between institutions. Most of the children had been finally placed before their first birthday No difference in adjustment was found between children who had stayed at an infant's home and those who had not. Among the girls who had done so, however an association was found between adjustment scores and a stay of more than six months, the correlation being significant at the 0 01 level when calculated for all the girls in the three groups. No association with the duration of institutional care was found for the boys. It is conceivable that selective factors connected with placement underly the association in the case of the girls, in that those with a poorer prognosis were not released so early from the home or that those with a longer stay were placed in less favourable environments than those who were placed early But it is difficult to explain why such selective factors should apply only to girls. Such factors as premature birth and complications during pregnancy and birth had no selective influence on the placement of the girls. There is therefore reason to interpret the association between the girl's adjustment scores and the time they spent at an infant's home as a causal connection. This could then be taken to reflect a constitutional difference between the sensitivity of boys and girls to experiences during infancy

Criminality and abuse of alcohol registered as indicated offences, were heavily over represented among the biological fathers, most in Group III and least in Group I Since the majority of children were living apart from their biological father there was some possibility of assessing the relative importance or heredity and environment for the adjustment of the child. No association between registered criminality and adjustment was found among the adopted children in Group I or among the boys in Groups II and III The girl's adjustment scores, on the other hand, co-varied with their father's criminality in Group II as well as in Group

III and thus correlation proved significant ($p < 0.05$) when the girls in these two groups were combined. There was thus a markedly significant difference ($p < 0.01$) between the boys and the girls in their relation to criminality among the fathers. A similar association was found between the girls adjustment and registered abuse of alcohol among the biological fathers but this was not significant. The results appear to support the hypothesis that psychiatric and nervous symptoms among girls are genetically conditioned more frequently than they are among boys, a theory that has been discussed by Rutter (1970) and others.

Although it has not been possible to find complete answers to the questions framed above, the results undoubtedly demonstrate that children whose conception is unwelcome are more prone than other children to display behavioural disturbances and problems regardless of the type of environment in which they grow up. Institutional care during infancy and hereditary factors also appear to have some bearing on the adjustment of the girls but not apparently in the same way for the boys.

The results concerning genetic relationship, however rest on a fairly weak foundation and these conclusions must be regarded as tentative. They nevertheless appear to warrant further investigations, partly along the same lines (that is concerning children or adults who have been separated from their biological environment at an early age) in order to analyze the extent to which symptoms of social insufficiency can be traced back to constitutional factors.

ACKNOWLEDGEMENTS

This study was made possible by generous research grants from the Child Welfare Committee of Stockholm. The Swedish Board of Medical Research and the Swedish Social Welfare Association made grants for translation and printing. Anne Wickström-Stormats, Socionomist, and Kerstin Ljunggren have been of invaluable help in collecting the material and processing the data. Statistical analyses were made by fil kand Kenneth Berglund and my contact with the IBM computer was made successfull by Associate Professor Anders Kajland. Rune Cederlof Associate Professor deserves many thanks for reading the manuscript and for stimulating criticism. Finally I wish to thank Patrick Hort, M.A., for translating my Swedish into English.

Stockholm, August 1971

Michael Bohman

Address
Child and Youth Psychiatric Department
St. Göran s hospital
Box 12500
112 81 Stockholm
Sweden

REFERENCES

AINSWORTH, M. D. (1962) The effects of maternal deprivation. A review of findings and controversy in the context of research strategy. In: Deprivation of maternal care. Public Health Papers 14. WHO Geneva.

BERFENSTAM, R. & VILLNER, L. (1966) Ensam mor i 60-talets samhälle. I—II. Socialmedicinsk Tidskrift, 7—8.

BLALOCK, H. M. (1960) Social Statistics. M. Gra Hill, London.

BOHMAN, M. (1970) Adopted children and their families. Proprius, Stockholm.

BOWLBY, J. (1951) Maternal care and mental health. WHO Monograph Series 2, Geneva.

BOWLBY, J., AINSWORTH, M., BOSTON, M. & ROSENBLUTH, D. (1956) The effects of mother child separation. A follow-up study. Brit. J. med. Psychol. 29, 211—47.

CLARKE, A. D. B. (1968) Problems in Assessing the Late Effects of Early Experience. In: Foundations of Child Psychiatry. Em. Miller (Ed.) Pergamon Press, Oxford — London.

COWIE, J., COWIE, V. & SLATER, E. (1968) Delinquency in girls. Heineman, London.

FRAIBERG, S. (1968) The origins of human bonds. Commentary.

GOLDFARB, W. (1943) The effects of early institutional care on adolescent personality. J. exp. Educ. 12, 106—129.

HEDQVIST (1969) Personal communication.

HESTON, L. L. & DENNEY, D. (1968) Interaction between early life experience and biological factors in schizophrenia. In: ROSENTHAL, D. & KETY, S. S. (Eds) The transmission of schizophrenia. Pergamon Press, p. 363—76.

HOLM, Å. (1968) Klasstabiller läsåret 1968—69. Elever och klassantal m.m. Stockholms skolor den 15 september 1968. Stockholms skoldirektion, mimeograph.

HUSÉN, T. (1969) Talent, Opportunity and Career. Almqvist & Wiksell, Uppsala.

HÖÖK, K. (1963) Refused abortion. Acta Psychiat. Scand. Suppl. 168, Vol. 39. Munksgaard, Copenhagen.

ILLSLEY, R. (1967) A sociological study of reproduction and its outcome. In: RICHARDSON, S. A. & GUTTMACHER, A. F. (Eds) Child bearing, sociological and psychological aspects. Williams & Wilkins, Maryland, p. 45—135.

JONSSON, G. & KÄLVESTEN, A. L. (1964) 222 Stockholmspojkar. Almqvist & Wicksell, Uppsala.

JONSSON, G. (1967) Delinquent Boys. Acta Psychiat. Scand. Suppl. 195, Vol. 43. Munksgaard, Copenhagen.

KADUSHIN, A. (1966) Reversibility of trauma. A follow-up study of children adopted when older. Unpublished mimeograph. Sixth International Congress of Child Psychiatry. July 24—29. 1966, Edinburgh.

KÄLLÉN, B. & WINBERGH, J. (1968) A Swedish register of congenital malformations. Pediatrics, Vol. 41, 4.

MUNRO, A. (1965) Childhood Parent-loss in Psychiatrically Normal Population. Brit. J. prev. soc. Med. 19 p. 69—79.

OTTERSTRÖM, E. (1946) Delinquency and children from bad homes. Acta Paediat. Vol. 33, Suppl. 5.

PASAMANICK, B., ROGERS, M. & LILIENFELDS, A. M. (1956) Pregnancy experience and the development of behaviour disorders in children. Amer. J. Psych. 112, 613.

ROBINS, L. N. (1966) Deviant children grown up. A sociological and psychiatric study of sociopathic personality. The Williams & Wilkins Company, Baltimore.

ROE, A. & BURKS, B. (1945) Adult adjustment of foster children of alcoholic and psychotic parentage and the influence of foster home. Memoirs of the section of alcoholic studies no. 3. Yale University. New Haven.

ROSENTHAL, D. (1970) Genetic Theory and Abnormal Behaviour. Mc Graw Hill.

RUTTER, M. (1970) Sex differences in Children. Responses to Family Stress. In: The international year book for children psychiatric and allied discipline. Vol. 1. 1970. "The child in his family". Anthony & Koupernick, (Eds).

SCHULSINGER, F. (1971) Psychopathy—Heredity and Environment. To be published in: International Journal for Mental Health.

SIEGEL, S. (1965) Nonparametric statistics for the behavioural sciences. Mc Graw Hill, Tokyo.

SKEELS, H. M. (1965) Effects of adoption on children from institutions. Department of Helath, Education and Welfare, Children, 12, p. 33—34.

SPITZ, R. A.(1945) Hospitalism. Psychoanalytic Study of the Child, 1, 53

SPITZ, R. A. & WOLFF K. M. (1946) Anaclitic Depression. Psychoanalytical Study of the Child, 2, 313.

STATENS OFFENTLIGA UTREDNINGAR (S.O.U.) (1951 43) Statistiska undersökningar kring alkoholfolgan.

STOTT D. H. (1969) The child' hazards in utero. p. 19—60 In HOWELLS, J G. (Ed.) Modern perspectives in international child psychiatry Oliver & Boyd, Edinburgh, London.

VINCENT C. E. (1961) Unmarried mothers. New York, The Free Press of Glencoe.

WERNER, E., SIMONIAN B S., BIERMAN, J M. & FRENCH, E. F (1967) Cumulative effect of perinatal complications and deprived environment on physical, intellectual and social development in preschool children. Pediatrics, Vol. 39 4.

WOOTTON, B. (1959) Social science and social pathology London, Allen & Unwin.

YARROW L. J (1965) Theoretical implications of adoption research, p. 45—58. In Perspectives on adoption. Child Welfare League of America, monograph.

ØYEN, E. (1966) Ugifte mødre. Universitetsforlaget, Oslo.

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

161. Peltonen, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 21.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glasser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966
167. Frenning, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children. Longitudinal Study. Sw. kr. 21.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Ballmer, Margret, Studies on Enuresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 30.— 1966
172. *Festschrift in Memory of Constantin Choremis.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersson, Per Ove, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 21.— 1967
175. Hirvonen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 21.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen. 1967. Sw. kr. 35.— 1967
178. Ekberg, Inger, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 23.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jürgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Gösta, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F., and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 23.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 23.— 1968
185. Andersen, Else, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 23.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1969
188. Mortensen, Ommund W. and Mahe, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 23.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Härnklint, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Kiseliker, Antti, Cardiovascular Responses of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kemppainen, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thoren, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Kasberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969
197. Sandin, Rune, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Villikidi, Ekko, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Snyder, Don M., Cravioto, Joaquin, Ramírez, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette E., Hartroft, Phyllis, Balis, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatus and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr, L., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Child-psychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 35.— 1970
210. Kasberg, Georg, Parental Attitudes to Pediatric Hospital Admissions. Sw. kr. 23.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 23.— 1971
212. Haltalina, Aipo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 33.— 1971
213. Lundstrom, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971
214. Samuelson, Gösta, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 23.— 1971
215. Bergström, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr. 23.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposia, Stockholm, August 30–September 1, 1970.* Edited by Claes Thorén. Sw. kr. 35.— 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 35.— 1971
219. Jaffé, Doris, Hartroft, Stanley, Manning, Mary and Eleta, Graciela, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. Sw. kr. 23.— 1971
220. Hallman, Nils, Bäckström, Leena, Kantero, Riitta-Liisa and Tiisala, Ritva, Studies on Growth of Finnish Children from Birth to Ten Years. 1971
221. Bohman, Michael, A Comparative Study of Adopted Children, Foster Children and Children in Their Biological Environment Born after Undesired Pregnancies. Sw. kr. 23.— 1971

Price Swed. kr 25.—

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 222 197

PLASMA MAGNESIUM LEVELS DURING THE FIRST FIVE DAYS OF LIFE

BY ERKKI JUKARAINEN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

From the Department of Pediatrics, University of Oulu Finland,
Head Professor Ole Wasz Hockert, M.D

PLASMA MAGNESIUM LEVELS DURING THE FIRST FIVE DAYS OF LIFE

By

ERKKI JUKARAINEN

Page 43, ERRATUM
right column, line 12 to transient hypercalcemia. This effect Correct to transient hypocalcemia. This effect

HELSINKI 1971

Supplementum 222 to
Acta Paediatrica Scandinavica 1971

Lukukirjapaino Oy   Helsinki 1971

Contents

INTRODUCTION — 5

REVIEW OF THE LITERATURE — 6

1. Plasma magnesium (Mg) — 6
2. Functions of magnesium — 9
3. Regulation of plasma magnesium — 10
4. Magnesium metabolism during pregnancy — 14

PURPOSE OF THE PRESENT STUDY — 17

PATIENTS AND METHODS — 18

RESULTS — 22

1. Magnesium concentration [Mg] in venous cord blood — 22
2. Relationship between plasma [Mg] and gestational age — 22
3. Relationship between plasma [Mg] and birth weight — 23
4. Relationship between plasma [Mg] and acid-base balance — 23
5. Plasma [Mg] in various groups of neonates — 26
   - *Normal control group* — 26
   - *Asphyxia groups* — 26
   - *Infants of diabetic mothers* — 27
   - *Infants of mothers with previous abortions* — 27
   - *Infants with gestational age less than 35 weeks* — 27
   - *Low birth weight infants of toxemic mothers* — 28
   - *Infants with birth weight of 4050—4620 g* — 28
   - *A case of congenital nephrosis* — 28
   - *Factors unrelated to significant deviations of plasma [Mg]* — 29
6. Relationships between concentration of plasma magnesium, serum calcium, and serum phosphorus — 30
   - *In preterm and term infants* — 30
   - *In low birth weight and full birth weight infants* — 31
   - *In infants of diabetic mothers* — 33
   - *In low birth weight infants of toxemic mothers* — 34
   - *In the neonate with congenital nephrosis* — 34
   - *Correlations of plasma [Mg] with serum [Ca] and serum [P]* — 35
7. Relationship between plasma [Mg] and blood glucose — 35

DISCUSSION — 37

1. Patients and methods — 37
2. Relation of gestational and neonatal factors to plasma [Mg] — 38
   - *Gestational factors* — 38
   - *Perinatal factors* — 39
   - *Postnatal factors* — 40
3. Acid-base disturbances and plasma [Mg] — 42
4. Interrelations of magnesium with calcium, phosphorus, and glucose — 43
   - *Relations with calcium and phosphorus* — 43
   - *Relation with blood glucose* — 45

SUMMARY — 46

ACKNOWLEDGEMENTS — 48

REFERENCES — 49

APPENDIX — 55

Introduction

Magnesium is the fourth most abundant cation in the body and the second most plentiful intracellularly. During recent years much has been added to the knowledge of normal human magnesium metabolism and its alteration in disease. This has ensued largely because of the advances made in the quantitative analysis of this element in biologic samples. Instrumentation of the recently developed atomic absorption spectroscopy provides a means for general use whereby multiple determinations of minute amounts of magnesium can be reliably made on small samples in a short time.

Magnesium has important biological and physiological activities. It is an activator of most of the enzymes involved in phosphorus metabolism and it acts as an agent in mitochondrial oxidative phosphorylation. Magnesium and calcium have complex interdependent influences on the excitability of the components of the neuromuscular apparatus.

As in the case of potassium, plasma magnesium concentration represents only a very minute portion of the total body content of this element. This small part, however, has been demonstrated to change markedly in certain clinical states, e.g. in renal disorders, reflecting disturbances of magnesium metabolism. Thus, although plasma Mg concentration does not reflect the total body Mg content, it seems obvious that valuable information about magnesium metabolism can be obtained from plasma Mg levels.

Investigations of Mg metabolism in adults as well as in animal experiments have elucidated the main principles of Mg metabolism in a normal condition and in various disease states. Marked similarities have been shown to exist between the metabolism of magnesium and calcium.

In recent years renewed studies of Mg metabolism have also been made on infants and children. Several reports have been published of clinical disorders associated both with hyper- and hypomagnesemia also in the neonatal period. Tetany induced by hypomagnesemia has been observed in the newborn. Untoward effects of hypermagnesemia in neonates of toxemic mothers receiving $MgSO_4$ therapy have been reported. While the changes of serum calcium levels in term and preterm newborn infants, as well as in infants with different neonatal disorders, have been well established, the behaviour of magnesium has been only incompletely studied. However, magnesium obviously plays a considerable part in the mineral metabolism already in the newborn period.

A neonate, especially if born prematurely, shows some metabolic qualities which are different from those of the normal healthy adult. Several enzymatic and hormonal mechanisms are not fully developed and there is anatomical immaturity as well. As a manifestation of these findings, the newborn has, among other things, renal functional incapacity, transitory parathyroid insufficiency and a lower blood pH than older subjects. Since it has been observed that magnesium metabolism in adults and in animal experiments is markedly affected by the above mentioned abnormalities, it seemed reasonable, both from the clinical and theoretical point of view, to study magnesium metabolism during the early neonatal period.

The object of the present study was to shed some light on the problems of magnesium metabolism during the first five days of life by determining the levels of plasma magnesium.

Review of the literature

1 PLASMA MAGNESIUM (MG)

The adult human body contains approximately 2 000 mEq of magnesium (178) while a newborn baby weighing 3.5 kg has about 60 mEq magnesium in his body (179) In adults, about half the total body magnesium is contained in bone, the remainder being almost equally distributed between muscle and nonmuscular soft tissues (3) Only 1 per cent of the total body magnesium is in the extracellular fluid and of that amount about 25 per cent is in the plasma. According to Walser (171) 32 per cent of adult plasma Mg is protein bound free magnesium concentration averages 55 per cent of the total and Mg phosphate, citrate and unidentified complexes account for 13 per cent. Teh (153) found an average of 68 6 per cent of ultrafiltrable magnesium in newborn infants

Owing to the multiplicity of imprecise methods for the determination of magnesium, normal plasma (or serum) values have varied over a wide range. A general survey of previous investigations of plasma (serum) Mg levels is presented in Tables 1 and 2

TABLE 1

SUMMARY OF THE LITERATURE ON PLASMA (SERUM) MAGNESIUM LEVELS EXCLUDING THE RESULTS OBTAINED BY ATOMIC ABSORPTION SPECTROPHOTOMETRY

Author	Year	Method	Material (number of observations)	Mean mEq/l	SD or Ranges
Bogert & Plass (20)	—31	Phosphate precipitation	Mothers (23)	1 6	1.2—2.6
			Cord blood (23)	1 7	1.2—2.8
			Adults (8)	1 9	1 6—2.2
Marloni & al. (107)	—31	Phosphate precipitation	Mothers (30)	1 48	0.99—1.81
			Cord blood (31)	1.51	1 05—1 94
Stutzman & Amatuzio (151)	—52	Phosphat precipatation	Adults (44)	1 95	±0.21
Salmi (140)	—54	Phosphate precipatation	Mothers (32)	2.20	1.4—2.9
			Arterial cord blood (28)	2.26	1.2—3.3
			Venous cord blood (37)	2.26	1.2—3.4
			Newborn 1—6 days (14)	2.46	1 9—3.3
			Children 1—2 months (20)	1.55	1 1—1.9
			Adults (10)		1 4—2.4

Brunelli & al. (26)	—66	Phosphate precipitation	Mothers (36)	1.52	±0.32
			Toxemic mothers (16)	1.42	±0.46
			Cord blood, normal pregnancy (36)	1.49	±0.34
			Cord blood, toxemic pregnancy (16)	1.42	±0.46
Orange & Rhein (125)	—51	Titan yellow	Newborn, first week (12)	1.63	1.3—1.9
			Older children (12)	1.78	1.6—2.0
			Adults (45)	1.87	1.6—2.1
Breton & al. (24)	—60	Titan yellow	Cord blood	2.76	1.78—3.3
			Children 1—24 months	2.12	1.5—2.6
			Older children	2.12	1.6—3.0
Anast (8)	—64	Titan yellow	Cord blood (41)	1.55	1.05—2.02
			First week (238)	1.58	1.12—2.38
			Children 1—12 months	1.68	1.48—1.98
			Older children	1.60	1.24—2.12
			Adults	1.65	1.12—1.94
Gittleman & al. (70)	—64	Titan yellow	Newborn, first day (156)	1.6	±0.16
Żytkiewicz & al. (183)	—65	Titan yellow	Mature newborn, II day (20)	2.40	1.78—3.17
			Premature, II day (21)	1.34	0.83—1.71
			Mothers (41)	1.71	±0.20
Bajpai & al. (11)	—66	Xylidylblue	Cord blood (15)	1.64	±0.12
			Newborn, I week (56)	1.51	1.20—1.80
			Older children (64)	1.82	±0.14
Haralambie & Keul (82)	—69	Xylidylblue	Adults (21)	1.81	±0.13
May & Keele (110)	—61	EDTA	Cord blood (23)	1.58	±0.18
			Children 1—2 months (18)	1.28	±0.13
			Older children (195)	1.35	±0.19
			Adults (15)	1.56	±0.19
Wacker & al. (166)	—57	Flame emission spectrophotometry	Adults (14)	2.05	±0.18
Alcock & al. (5)	—60		Adults (6)	1.66	±0.01
					1.45—1.85
MacIntyre (103)	—63		Adults		1.5—1.8
Macpherson (105)	—65		Adults	1.84	±0.21
Schachter (143)	—59	Fluorometry	Adults (33)	2.03	±0.22
Kobayashi (97)	—67	Fluorometry	Newborn 0—5 day (13)	1.64	±0.19
			Infants 6—10 days (9)	1.53	±0.15
			Infants 11—30 days (16)	1.68	±0.16
			Children 31—60 day (6)	1.78	±0.17
			Children 2—11 months (23)	2.26	±0.15
			Children 1—5 years (40)	2.25	±0.16
			Children 6—15 years (15)	2.16	±0.17
Teh (153)	—68	Fluorometry	At birth (18)	1.53	0.050[1]
			Newborn first week (20)	1.35	0.046[1]
			Infants 2—4 weeks (13)	1.34	0.095[1]
			Children 2 months—2 years (12)	1.64	0.071
			Children 2 years—10 years (13)	1.68	0.054[1]
			Young adults (21)	1.90	0.036

[1] Standard error

TABLE 2.

SUMMARY OF THE LITERATURE ON PLASMA(SERUM) MAGNESIUM LEVELS BY ATOMIC ABSORPTION SPECTROPHOTOMETRY

Author	Year	Material (number of observations)	Mean	SD or Ranges
Stewart & al. (150)	—63	Adult	1.74	
Wacker & al. (168)	—64	Adults (10)	2.14	±0.17
Giese (61)	—66	Adults	1.76	±0.21
Girard & al. (64)	—66	Adults	1.81	±0.25
Iida & al. (91)	—67	Adults	1.81	±0.18
Harrison (83)	—68	Premature infants	1.40	±0.08
		Newborn full-term	1.50	±0.05
		1—10 years	1.86	±0.06
		Adults	1.99	±0.04
Fomon & al. (52)	—69	Infants, age 28 days, female (39)	1.7	±0.3
		Infants, age 28 days, male (40)	1.7	±0.2
		Infants, age 56 days, female (32)	1.7	±0.2
		Infants, age 56 days, male (47)	1.7	±0.2
		Infants, age 84 days, female (40)	1.7	±0.2
		Infants, age 84 days, male (43)	1.7	±0.2
		Infants, age 112 days, female (41)	1.7	±0.2
		Infants, age 112 days, male (50)	1.8	±0.2
Harvey & al. (85)	—70	Newborn, 1 day (16)	1.07	0.74—1.32
		First week, breast-fed (31)	1.10	0.76—1.41
		First week, bottle-fed (58)	0.97	0.76—1.23
Tsang & Oh (160)	—70	Low birth weight (<2000 g) infants 0—5 days	1.86	±0.28
Engel & Elin (47)	—70	Cord blood		
		Apgar 8—10 (67)	1.59	±0.28
		Apgar 6—7 (12)	1.77	±0.19
		Apgar < 6 (11)	1.95	±0.4

In the studies of Salmi (140) and Żytkiewicz & al. (183) in which both the plasma Mg levels of the first week and those of older children or adults were determined the values of the first week were found to be higher than those of older children and adults. In the studies of Orange & Rhein (125) Anast (8) Bajpai & al (11) Kobayashi (97) Teh (153) and Harrison (83) the Mg levels for the first week were found to be lower than those of older children. Salmi Orange & Rhein, Teh and Harrison found the Mg levels in children to be, on average, lower than those in adults Żytkiewicz & al and Harrison found the Mg levels to be lower in premature than in mature infants during the first week of life. These values were also lower than in adults.

A gradual rise in serum [Mg] during the first week of life has been observed by Anast (8) Harvey & al. (85) and Gittleman & al. (70) in mature newborn infants on breast milk. The same tendency was also found by Tsang & Oh (160) in low birth weight infants during the first five days. In the study of Bajpai & al. (11) there was a slight, but insignificant tendency for serum Mg levels to decrease during the first week. They did not find any difference between breast fed and bottle-fed infants, while Harvey & al. (85) and Anast (8) showed that serum Mg levels were significantly lower at the end of the first week when the baby was

bottle fed. Gittleman & al found that infants fed a processed milk formula supplemented with 60 units of vitamin D daily had significantly lower magnesium levels at 5 days than on the first day of life, while with a processed milk formula without vitamin D no difference was found.

Magnesium unlike calcium, showed no initial drop in serum levels during the first 24 to 48 hours, according to the studies of Tsang & Oh (160) Harvey & al. (85) and Bajpai & al (11) In low birth weight infants, Tsang & Oh found that small for gestational age infants had significantly lower Mg levels than appropriate for gestational age infants throughout the first five days of life.

2. FUNCTIONS OF MAGNESIUM

In 1968 Wacker & Parisi (169) presented an elaborate review of magnesium metabolism. Their report was the main source of reference for the following section

Influence on enzyme systems Magnesium is an activator *in vitro* of a great number of enzyme systems that are vital to cellular metabolism. Prominent among these are the enzymes that hydrolyze and transfer phosphate groups, including the phosphatases and those concerned in the reactions involving adenosine triphosphate. Since adenosine triphosphate (ATP) is required for the utilization of glucose, fat, protein, nucleic acid, and for coenzyme synthesis muscle contraction methyl group transfer sulphate, acetate and formate activation, an interference in the activating effect of magnesium extends to all these functions (169)

In addition magnesium is required as a cofactor for oxidative phosphorylation *in vitro* (99 130 131) Attempts to demonstrate an *in vivo* counterpart of this requirement in mitochondria obtained from magnesium-deficient animals have led to conflicting results (15 165)

In mammalian cells, important observations have been made that are in keeping with the known *in vitro* requirement of magnesium both as an activator of most of the enzymes involved in phosphorus metabolism and as an agent in mitochondrial oxidative phosphorylation. It has been found that the higher the metabolic activity of the cell, the greater the ratios $[Mg^{++}]/[Ca^{++}]$ and $[K^{+}]/[Na^{+}]$ Another striking relation obtains between the intracellular concentration of magnesium and the content of phosphorus. As the intracellular content of magnesium and calcium increases (magnesium representing the major part of this sum) from inactive tissues, such as skin and erythrocytes, up to very active tissues, such as liver brain and striated muscles, there is a concomitant increase in the cellular content of phosphorus (169)

Magnesium is further involved in protein synthesis by contributing the binding of messenger RNA (ribonucleic acid) to the 70 S ribosome (23 74) Magnesium is also required for the *in vitro* synthesis (48) and degradion of desoxyribonucleic acid (DNA) (98) and it is also included in all the amino acid activating systems (89 109)

Magnesium has an important role in the formation and preservation of large ribosomes. The aggregation or dissociation of component particles in ribosomes obtained from *Escherichia coli* (157 158) baker's yeast (32) pea seedlings (161) rat liver (78) and rabbit reticulocytes (43) is vitally dependent on the ambient magnesium concentration.

Magnesium contributes significantly to macromolecular structure. The intricate organization of DNA (42, 163), RNA, and ribosomes (137 158) is stabilized by the presence of this metal.

Physiological and pharmacological features Magnesium and calcium have complex interdependent influences on the excitability of the component of the neuromuscular apparatus. Magnesium or calcium depletion leads to increased neuronal excitability and enhanced neuromuscular transmission. In muscle, however the effect of calcium and magnesium are antagonistic. Low concentrations of magnesium lower the excitatory thresholds of the presynaptic nerve and of the muscle membrane, but increase the liberation of acetylcholine. Low concentrations of calcium

also lower the excitatory thresholds of the presynaptic nerve and of the muscle membrane but, unlike magnesium, decrease the liberation of acetylcholine (46 162)

In pharmacological doses magnesium has a curariform action on the neuromuscular junction, presumably by interfering with the release of acetylcholine from motor nerve terminals (96) Magnesium is a potential anticonvulsant and anesthetic agent (129)

Cardiac conduction is affected at serum concentrations of 5 to 10 mEq/l, resulting in increases of the PR interval and QRS duration and increased height of the T wave in the ECG Deep tendon reflexes are lost when the serum magnesium concentration approaches 10 mEq/l, and respiratory paralysis occurs near 15 mEq/l. General anesthesia may occur at concentrations close to those required to produce respiratory paralysis. Extremely high serum concentrations (in excess of 25 mEq/l) cause cardiac arrest in diastole (169) Symptomatic hypermagnesemia occurs most frequently in patients with renal failure. Deleterious effect of hypermagnesemia on the newborn, secondary to maternal $MgSO_4$ therapy, have been described (101 102) Respiratory failure and hyporeflexia have resulted.

Tetany the most distinctive symptom in the course of magnesium depletion can occur when hypomagnesemia exists in the absence of other measurable serum electrolyte or acid base abnormalities. Recognition of this fact led to the definition of the human magnesium—deficiency tetany syndrome as a specific clinical entity (162) The tetany may be either overt or latent It is promptly reversed by administration of magnesium, but not by calcium (37 167 181) Magnesium deficiency may be manifested by other neuromuscular dysfunctions besides tetany such as generalized tonic-clonic as well as focal seizures, ataxia, vertigo muscular weakness, tremors, and sometimes by behavioral disturbances such as depression, irritability and psychotic behaviour All these disturbances are reversed by magnesium administration

Significant hypocalcemia and hypomagnesemia may coexist, particularly in patients with excessive loss of gastrointestinal fluids. Most of the patients with symptomatic magnesium deficiency have serum concentrations of magnesium less than 1 mEq/l. However tetany or other overt manifestations of magnesium deficiency do not develop in all patients with such low concentrations. Among potentially critical factors still to be fully evaluated the amount of serum magnesium bound to protein and the concentration of magnesium within cells may be mentioned (162) In hypomagnesemic tetany depression of the ST segment and inversion of the T waves can be seen in the precordial leads of the ECG

A number of patients with documented but otherwise unexplained hypomagnesemia have been described and it has been suggested that this defect may occur on a familial basis (54 56 65) Some of these patients were newborn infants and had convulsions associated with hypocalcemia and hypomagnesemia. The seizures could not be prevented by giving calcium, but on the oral administration of magnesium supplements symptoms were controlled, and both hypomagnesemia and hypocalcemia disappeared (41 56 128, 121 139) Continued supplementary magnesium therapy enabled the infants to remain free from seizures and to develop normally

Osmotic role Because of its low concentration in the extracellular fluid, the part played by magnesium in maintaining the osmotic pressure can only be small (about 1/300 of the total osmotic pressure in the plasma) (149)

3 REGULATION OF PLASMA MAGNESIUM

Absorption and excretion. The average daily magnesium intake of a human adult on a normal diet is of the order of 25 mEq (93) Requirements for children are higher and during pregnancy the need is also increased (156) In severe and chronic intestinal disorders and malnutrition hypomagnesemia has been encountered (13 21 31 72, 138, 142) The human infant, if breast fed receives substantially less magnesium than when bottle fed. His ability

to retain the magnesium which he absorbs is also less than when on cow's milk, apparently because the lower phosphate content of human milk limits the deposition of calcium and magnesium in the bone (177). It has been shown by several investigators (8, 70, 85) that newborn breast fed infants have higher plasma Mg levels than bottle fed infants. The mean percentage of magnesium in human milk is about 1.9 mEq/kg while that of cow's milk is 11.5 mEq/kg (111, 145).

Stool content varies with intake and with the dietary content of anions, particularly phosphate. Calcium also influences the amount of magnesium absorbed, apparently by competition for a common absorptive pathway (6). Little endogenous magnesium is eliminated by the fecal route under ordinary circumstances.

Normally about a third of the ingested magnesium is absorbed and excreted in the urine. The organ which regulates the body's content of magnesium, is, above all, the kidney. Increased urinary output of magnesium follows an increase in dietary magnesium, despite the absence of any detectable change in plasma magnesium concentration (88). Conversely magnesium deprivation in man is followed by a prompt reduction of urinary magnesium to very low levels, despite the absence of a detectable fall in plasma magnesium concentration (14, 51). Animal studies have shown that the site of active reabsorption of magnesium is in the proximal portion of the distal nephron. A tubular secretory mechanism could not be documented (118).

Normal values of urinary magnesium excretion calculated by Evans & Watson (49) suggest an upper limit of 2 mg per kg per day. A similar value for children is proposed by O'Brian & Ibbott (124). Under conditions of magnesium deprivation the normal kidney is able to conserve magnesium, restricting excretion to as little as 1 mEq per day (14).

Decreased serum concentrations of magnesium have been observed in patients with renal disease, including glomerulonephritis, hydronephrosis, pyelonephritis, nephrosclerosis, and renal tubular acidosis (169). With more advanced renal disease associated with azotemia, hypermagnesemia usually occurs. In general, the degree of hypermagnesemia correlates with the magnitude of nitrogen retention (148). Hypermagnesemia also occurs in acute renal failure (166).

Hormonal control of plasma magnesium levels. It has long been known that there is magnesium loss during active hyperparathyreoidism, a positive balance occurring upon the removal of a parathyroid adenoma (169). Plasma magnesium is normally maintained by the body within very narrow limits. There is much evidence, based on mainly animal experiments, to suggest that the homeostatic mechanism of plasma magnesium is a variation in the secretion of *parathyroid hormone* in response to changes of plasma magnesium (10, 29, 45, 63, 66, 67, 104, 126). This implies that a rise in plasma magnesium will inhibit the secretion of parathyroid hormone, producing an increased excretion of magnesium in the urine and a return of the plasma level towards normal. A fall in plasma magnesium will stimulate the production of parathyroid hormone, leading to increased renal conservation. This also implies that calcium and magnesium homeostasis are interdependent and that calcium homeostasis will not be maintained in the face of marked abnormalities in plasma magnesium.

In their study on the effect of parathyroid extract on magnesium in man, Gill & al. (63) found that parathyroid extract can increase the tubular reabsorption of magnesium and calcium but its predominant effect is to increase the renal excretion of these ions, presumably by releasing them from body tissues such as bone. Whereas magnesium excretion can be altered by parathyroid extract, normal serum values in the patients with hypoparathyroidism suggest that this ion, unlike calcium, is not dependent on the parathyroid glands for its regulation.

Jones & Fourman (94) found significantly lower mean plasma magnesium concentration than normal in patients with parathyroid insufficiency. The urinary excretion of magnesium was also less than normal. They found that the in-

fusion of magnesium reduced the plasma calcium in patients with parathyroid insufficiency as well as in normal persons. The fall in plasma calcium produced by magnesium infusion cannot be the result of a simple inhibition of parathyroid secretion.

It is not yet clear whether the parathyroid hormone affects magnesium directly or only through its action on calcium metabolism. Gitelman & al. (67) showed however that magnesium deficient parathyrectomized rats did not have a higher level of calcium in plasma than their nondeficient controls, while magnesium-deficient rats with intact parathyroid glands developed significant hypercalcemia and hypophosphatemia and in addition, the concentration of ionic calcium in plasma was significantly elevated They concluded that the hypercalcemia and hypophosphatemia of magnesium deficiency demands parathyroid gland activity and that the regulation of this activity is modified in the magnesium-deficient state to permit the maintenance of an elevated concentration of ionic calcium in plasma. Moreover it has been shown in animal experiments that magnesium, like calcium influences the size and activity of the parathyroid gland and this indicates that parathyroids are involved in the endocrine control of magnesium metabolism (10)

The effect of parathyroid hormone on urine calcium is overshadowed by the effect of this hormone on bone. In the case of magnesium, however the renal effect may be more important, since the calcium-magnesium ratio in bone is 50 1 while the renal conserving effect of parathyroid hormone results in similar retentions of calcium and magnesium (104)

Three cases of hypomagnesemia associated with the early type of idiopathic hypoparathyroidism have been described (120, 152)

Thyrocalcitonin is known to produce hypocalcemia and hypophosphatemia. Most of the published evidence indicates that thyrocalcitonin does not modify the concentration of plasma magnesium in different animal species (16 53) Gudmundsson & al (75) found a slight reduction in plasma magnesium concentration in rats. Palmieri & al. (126) discovered a significant reduction of plasma magnesium concentration in intact rats and in animals pretreated with parathyroid extract after the administration of thyrocalcitonin. The reduction was thought to be related to an inhibition of bone resorption, the same mechanism that might be responsible for the hypocalcemic effect of thyrocalcitonin The reduction observed by Palmieri & al. was much smaller in the case of magnesium than it was for calcium (0.2 mg/100 ml and 3 0 mg/100 ml respectively) This is probably related to the lower content of magnesium in bone and to the fact that in bone resorption the rate of calcium removal usually exceeds that of magnesium. In the study of Palmieri & al. it was further found that the capacity of thyrocalcitonin to retard bone resorption was not impaired by parathyroid extract in fact, it appeared that thyrocalcitonin, in the dose administered was also capable of offsetting the increased bone resorption induced by parathyroid extract.

Palmieri & al. (126) found that *cortisone* completely abolished the hypomagnesemic effect of thyrocalcitonin while according to their earlier observations, cortisone could only partially inhibit the hypocalcemic response to thyrocalcitonin. The more effective inhibition by cortisone of the hypomagnesemic effect could be related to the surface location of magnesium in bone crystals. The effect of glucocorticoids on plasma magnesium is controversial, there is some evidence that cortisone increases plasma magnesium concentration, while the results of Palmieri & al did not confirm this observation

The connection between *aldosterone* secretion and magnesium homeostasis has been recognized for a long time (106 114) Hyperaldosteronism causes hypomagnesemia and magnesium levels are restored to normal by correcting the hyperproduction of aldosterone. Studies in rats have demonstrated that aldosterone causes increased excretion of magnesium in both urine and feces (81) In adrenal insufficiency the serum magnesium concentration

is increased (169) Changes in aldosterone secretion in response to corrected or overt magnesium deficiency indicating an inverse relationship to magnesium homeostasis, have not been found (35)

Vitamin D can influence magnesium balance. Meintzer & Steenbock (112) showed that vitamin D caused a slight, but significant, increase in the gastrointestinal absorption of magnesium in rat. The studies of Hanna (80) revealed a substantial decrease in fecal magnesium following the administration of large doses of vitamin D Similar results have been obtained in the pig (113)

Pharmacological doses have led to hypomagnesemia (60, 80 112 135 182) while two patients with hypercalcemia due to vitamin D intoxication had normal serum magnesium (172)

Anast (9) found that magnesium metabolism was unaltered in a 4-year-old boy with untreated vitamin D-resistent rickets. Treatment with 200 000 to 300 000 I U of vitamin D per day resulted in a decrease in the serum magnesium levels with no consistent changes in the urinary excretion, intestinal absorption, or retention of magnesium. The administration of 350 000 I U of vitamin D per day was associated with an increase in both the urinary excretion and intestinal absorption of magnesium. The effects of vitamin D on the intestinal absorption and urinary excretion of magnesium represent either primary actions or they are secondary to changes in calcium and phosphorus metabolism. The results of Anast also support the previously reported animal studies that the action of vitamin D causes a redistribution of magnesium in the body

The studies of Jones & al. (92) and Dimich & al. (39) indicate that *thyroid hormone* has a stimulatory action on the cellular transport of magnesium. Low plasma magnesium levels and negative magnesium balance in thyreotoxicosis have been demonstrated by several investigators (40, 170) Conversely patients with hypothyreosis tend to have elevated plasma magnesium concentrations and positive magnesium balance (92, 136) An inverse relationship has been found between body temperature and plasma magnesium in dogs (87 117) In hibernating animals a high plasma magnesium concentration has been found during hibernation (173)

Insulin and magnesium are said to have a synergistic effect (73) In his study with Mg^{28} in rabbits Aikawa (2) found no significant changes in serum magnesium or blood glucose when simultaneous injections of magnesium, insulin and glucose were given, but there was an increase in the uptake of Mg^{28} in all tissues studied. In skeletal muscle and heart there was a significant increase in magnesium content as well as in the Mg^{28} relative activity When insulin or dextrose alone was given following an injection of magnesium, similar significant changes were noted but were, however less marked.

Several studies have shown that plasma magnesium levels are elevated prior to the institution of therapy in diabetic coma (108, 119 169) It is thought that the rapid catabolism of uncontrolled diabetic acidosis causes this ion, as well as potassium and phosphorus, to move out of the cells into the extracellular fluid and plasma faster than they can be excreted by the kidneys, whose function is impaired by dehydration (119) It has been noticed that large amounts of magnesium are excreted during experimental diabetic acidosis (169) Within a few hours of commencing treatment the plasma level of magnesium falls below normal. This fall results from the movement of this electrolyte back into the cells and also from urinary loss as renal function returns with the correction of dehydration. Renal conservation of magnesium is soon highly effective and it almost disappears from the urine (119) Tetany has been observed when acidosis has been corrected without the use of supplemental magnesium (30)

Several investigators suggest that the metabolism of magnesium is intimately related to that of carbohydrate (2, 86) Magnesium has been shown to shift into the cells in carbohydrate anabolism in rat liver slice preparations (28) Studies on rabbits have shown that parenteral administration of magnesium may cause a temporary hyperglycemia (86) The intravenous injection of small amounts of

magnesium decreases the rate of removal of glucose from the blood

Hanna (79) has reported the effects of *growth hormone* on magnesium metabolism. In pituitary insufficiency when growth hormone was administrated, there was a rise in the intestinal absorption and urinary excretion of Mg and the plasma Mg concentration fell. These changes reverted to normal in a day or two. It is not known whether these vitamin D — like effects are primary or secondary

Effect of pH on plasma magnesium. As pointed out in connection with diabetic coma, uncontrolled diabetic acidosis is associated with elevated plasma magnesium concentration. This is thought to be due to the shift of this ion out of the cells (119). In the work of Gilbert (62) on frog muscles in vitro it was shown that both calcium and magnesium ions can contribute to the pH buffering of the extracellular phase by moving out of the muscle when the extracellular phase is acid and by moving into the muscle when the extracellular phase is alkaline. It is thought that changes in pH might influence the active transport mechanism of magnesium.

Whang & Wagner studied the influence of venous occlusion and exercise on serum magnesium concentration in man (176). They found elevated serum magnesium concentrations in the presence of decreased pH values. Metabolic acidosis was, however, discounted as a reason for raised magnesium levels because the magnitude of acidosis in this study did not approach that observed in the experimental situation and because the close parallel in the percentage changes in hematocrit, osmolality and serum Mg could be accounted for more readily by a shift of water into the cells.

Engel & Elin (47) found elevated cord blood magnesium levels associated with birth asphyxia. They also observed a rise in plasma magnesium concentrations in newborn dogs with acute anoxia.

4 MAGNESIUM METABOLISM DURING PREGNANCY

Very little is known about placental transfer of magnesium or its uptake in the fetal tissues. Aikawa & Bruns (4) studied these problems in near term pregnant rabbits with radioactive magnesium. They found that in pregnant rabbits there was a slower uptake in bone and muscle than in nonpregnant animals. Aikawa & Bruns found that the placental concentration of Mg^{28} became higher than the concentration in maternal plasma within 2 hours, suggesting that the placenta actively concentrates magnesium. It was further found that Mg^{28} rapidly crossed the placenta, and in spite of the lower magnesium concentration of fetal tissues, Mg^{28} uptake was rapid and increased progressively. The uptake of various fetal tissues was related to anabolic activities of the cells involved. The fetal tissues approached a constant value in 24 hours. Observations of the transfer of Mg from mother to fetus have been made when $MgSO_4$ has been used in the management of toxemia of pregnancy (101, 102). It has been shown that Mg crosses the placenta and causes hypermagnesemia in the fetus

In the direct analysis of the chemical composition of the human fetus, Givens & Macy (71) found that the deposition of magnesium differs from that of calcium. While it was found that the greatest calcium deposition is made in the last 3 months of fetal life, utilization of the average content of magnesium shows an increase up to the 8th month. During the last two months there appears to be no increase in the magnesium content per individual. It may be noted that the average percentage of magnesium in the total ash decreases slightly with the age of the embryo

Fee & Weil (50) studied body composition by the direct analysis of infants who were either stillborn or died in 10 days. In their series, 10 were the infants of diabetic mothers, their gestational age varying from 28 to 38 weeks and birth weight from 1 090 g to 3 450 g. There were 13 infants of nondiabetic mothers, with gestational age from 11 to 37 weeks and birth weight from 18.9 g to 2 060 g. They found no consistent change of magnesium concentration with age or weight (mEq/kg fat free wet weight) in either group

In a textbook of Pediatrics edited by Barnett, Weil (175) presents data, available in the literature, of the average composition of magnesium for the human fetus

Weight (g)	250	500	1000	1500	2500	3500
Age (weeks)	18	22	28	31	37	40
Magnesium in millimoles	1	3	6	10	16	23
Magnesium millimoles per kilogram (fat-free)	4	6	6	7	7	8

In terms of allometry a concept of relative growth which was introduced by J F Huxley and G Teissier (90 154) the relationships of growth can be expressed as $y = bx^k$ where y is the amount of one substance present at some time, b is a constant, x is the amount of the substance present at this time, and the exponent k is a constant representing the slope of the line. The allometric relation refers to the straight — line relationship between the logarithmic expressions of any two substances involved in growing organisms. It can be demonstrated that there is an allometric relationship between each of the major chemical components and the total weight of the human fetus, when related to the total fat-free wet weight of the organism. Figure 1 has been drawn so that the term b was constant for all substances, the difference in the lines being then due to their different k values. The substances group themselves into two categories those with k values greater than 1 which are substances increasing at a rate more rapid than the fat free weight of the individual and those with a k value less than 1 which are increasing at a rate less than that for the total fat-free weight of the individual. Magnesium has a k value of 1 155 compared with that of calcium 1.281 phosphorus 1.238, and potassium 1 114 Sodium, chloride and water have a k value of less than 1 This indicates that magnesium, a cation which is intimately associated with intracellular solids, increases more slowly than calcium and phosphorus, the main ions in bone salts, but more rapidly than potassium, the major cation of intracellular water

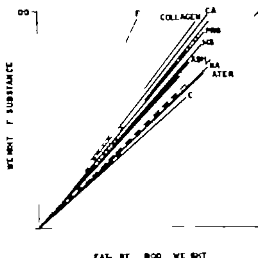


Fig 1 Relative values for k in $y = bx^k$ see text (From Weil W B., J Chemical composition of the fetus. In H. L. Barnett (ed.) Pediatrics. Butterworths, London Appleton-Century-Crofts, Division of Meredith Corporation, New York 1968, p 21) By courtesy of the publisher

Very little is known about factors regulating magnesium metabolism during pregnancy Norris (123) suggests that fetal parathyroids are functioning He reached this conclusion by studying the histology of the parathyroids of human embryos and fetuses. Scothorne (144) demonstrated that when the parathyroid glands from 12—13 week fetuses were transplanted onto chick chorioallantoic membrane in apposition to bone, they showed parathyroid activity attested by the resorption of the bone. The state of the maternal parathyroids, and abnormalities in the maternal calcium and phosphorus metabolism exert an influence on the fetal parathyroids and mineral metabolism. It has been demonstrated by many investigators (55 84 115) that maternal hyperparathyroidism has resulted in neonatal hypocalcemia. The suppression of fetal parathyroid activity is assumed to be due either to maternal hypercalcemia or to the excess parathomone

in the mother both moving easily across the placenta. Aceto & al. (1) and Bronsky & al. (25) have both described an infant with intrauterine hyperparathyroidism secondary to the mother's hypoparathyroidism. Sinclair (147) found that, in rats, fetal parathyroids are stimulated by maternal hypocalcemia induced by low calcium diets or parathyreoidectomy. Bodansky & Duff (19) showed that rat fetuses born to parathyreoidectomic mothers had a much lower content of calcium in their carcasses. It is not known whether physiological doses of vitamin D in the mother would be detectably distributed to the fetus but the administration of large doses of vitamin D to pregnant rabbits increased bioassayed antirachitic activity in the serum of the fetuses (57). It can be assumed that magnesium metabolism changes in the same direction as calcium in these situations, although no information is available. In a case of neonatal hypomagnesemia with convulsions associated with maternal hypophosphatemia, reported by Dooling & Stern (41) there were no other indications of maternal hyperparathyroidism.

Salmi (140) and Anast (8) found the magnesium concentration of cord blood to be lower than Mg levels during the first week of life. This possibly reflects the role of the placenta in magnesium metabolism in utero. Salmi did not find any difference in magnesium levels in blood obtained from the umbilical artery as compared to the umbilical vein. In the studies of Bogert & Plass (20), Marioni & al. (107), Salmi (140) and Brunelli & al. (26) no significant difference was found between cord blood and maternal serum magnesium concentrations. In the study of Lipsitz (101) cord blood serum Mg level was slightly higher than in the maternal serum in a normal uncomplicated pregnancy. Salmi, and Breton & al. (24, 140) found cord blood levels to be higher than those of older children and adults. Bogert & Plass (20), Mays & Keele (110) and Anast (8) found no difference in the magnesium levels of cord blood and in the blood of older children and adults. Bajpai & al. (11) found the Mg levels of cord blood to be somewhat higher than the levels of the first week of life.

Purpose of the present study

Knowledge concerning the Mg metabolism of the early neonatal period is far from complete.

The present study was an attempt to shed more light on this subject. The investigation was designed

I To study the relationships of plasma magnesium levels to gestational age and birth weight during the first five days of life.

II To establish the pattern of behaviour of plasma magnesium concentration at the age of 0—5 days of life, and to find out whether plasma magnesium levels in the newborn with some neonatal or maternal disorders show significant deviations from normal during the first five days of life.

III To study the relations of plasma [Mg] to serum [Ca] serum [P] and blood glucose levels during the first five days of life

2

Patients and methods

A hundred and eighteen neonates of the study were chosen from the newborn delivered between February 1969 and September 1970 in the Department of Obstetrics, University of Oulu, and from those who were referred to the neonatal unit Department of Pediatrics from regional hospitals. In August 1971 the study population was completed with 12 normal newborn infants, giving a total number of 130 In this district there are approximately 7 000 births per year

Clinical data on the maternal history labour delivery and neonatal course were recorded.

The patients were divided into groups according to gestational age, birth weight, mode of delivery neurological symptoms, and other disorders of the newborn. Out of the 130 neonates studied. a total of 30 infants, representing a random sample of normal newborn, constituted a normal control group. The pregnancies and deliveries had been without complications, the gestational age was 38—41 weeks, birth weight was over 2,500 g and the postnatal course was uneventful.

The patients included four twins, two unrelated twin partners, two infants of the same mother born with an interval of one year and four months, and one case of congenital nephrosis, diagnosed later

Clinical features of the study population are summarized in Table 3

TABLE 3.

CLINICAL DATA ON 130[1] NEWBORN INFANTS WHOSE PLASMA MAGNESIUM LEVELS WERE STUDIED. DISTRIBUTION OF PATIENTS INTO GROUPS.

Groups	Number of Infants	Number of Observations	Observations per Infant
Sex			
Female	61	524	8.6
Male	69	739	10.7
Total	130	1263	9.7
Gestational age			
28—32 weeks	5	42	8.4
33—34 weeks	9	92	10.2
35—36 weeks	16	180	11.3
37—38 weeks	19	157	8.3
39—40 weeks	54	535	9.9
41—44 weeks	27	257	9.5
Total	130	1263	9.7
Preterm infants of 28—36 weeks	30	314	10.5

[1] Including the supplement of 12 normal neonates, which was taken into account only in the normal control group.

Birth weight			
1020—1549 g	6	54	9.0
1550—2049 g	13	130	10.0
2050—2449 g	23	241	9.6
2450—3049 g	26	221	8.5
3050—3549 g	26	270	10.4
3550—4049 g	25	250	10.0
4050—4620 g	9	97	10.8
Total	130	1263	9.7
Low birth weight infants (<2500 g)	45	457	9.7
Small for date[1]			
Birth weight ≥ 2500 g	9	82	9.1
Birth weight < 2500 g	33	327	9.9
Total	4	409	9.7
Birth weight < 2500 g			
Small for date	33	327	9.9
Appropriate for gestational age	12	110	9.2
Total	45	437	9.7
Birth weight 2500 ≥ g			
Small for date	9	82	9.1
Appropriate for gestational age	76	744	9.8
Total	85	826	9.7
Asphyxia			
Intrauterine	21	157	7.5
Postnatal, 1 min Apgar ≤ 6 (12 infants also had signs of intra-uterine asphyxia)	28	230	8.2
Total	49	387	7.9
Caesarean section	26	263	10.1
Maternal factors			
Diabetes mellitus	9	96	10.7
Primiparity	58	578	10.0
II—V parity	60	576	9.6
≥ VI parity	12	109	9.0
Previous abortions	22	205	9.3
Neonatal disorders			
Neurological symptoms	31	264	8.5
Infections	9	92	10.2
Congenital nephrosis	1	11	11.0
Others	23	161	7.0
Total	64	528	8.3
Deaths	7	36	5.1
Normal control group	30	332	10.7

Birth weight below the 10th percentile of intrauterine growth curve (134)

All the newborn were fed on breast milk. Milk feeding was started on the second day glucose water (about 60 ml/kg/day) was begun at the average age of 12 hours. The newborn who had biochemical abnormalities of blood such as hypoglycemia, hypocalcemia, and acidosis received therapy. Infants with blood glucose ≤ 25 mg/100 ml were treated either with oral 10 % or intravenous 10—20 % glucose. Symptomatic infants with serum calcium value below 4.0 mEq/l and those without symptoms but with serum calcium ≤ 3.2 mEq/l were treated with oral and/or intravenous calcium gluconate. The acid base balance of the infants was determined when necessary by the micro-Astrup method (146). Metabolic acidosis was corrected with intravenous sodium bicarbonate according to the base deficit. This therapy was given without delay and effectively. Since it is known that blood acid base status is related to plasma Mg levels, metabolic alkalosis having a lowering effect (62, 176) the treatment of acidosis, without doubt, markedly modified plasma Mg levels in the 36 newborn of the study who had marked metabolic acidosis. The present investigation, however was not controlled with regard to the amount of sodium bicarbonate given. Some infants were given extra oxygen in the incubator and many received antibiotics intramuscularly.

Magnesium, as a treatment for toxemia, was not given to the mothers of the study patients.

Plasma Mg serum calcium, serum phosphorus and blood glucose determined from heel capillary blood samples were followed consecutively during the first five days. In 61 cases the first samples were obtained before the age of two hours. For the first three days two to three specimens were taken daily on the fourth day two samples and on the fifth, one. If the patient had an umbilical arterial catheter the samples were collected through it. A total of 1263 serial plasma magnesium determinations were performed during the study. On the first day 308 samples were obtained, on the second day 292 samples, and during the third to fifth day 662 samples. An average of determinations per infants during the five days was 9.7 on the first day the average was 2.4 on the second day 2.2, and from the third to the fifth day 5.1. In 22 cases Mg Ca, and P concentration of venous cord blood was also determined.

Determination of magnesium by atomic absorption spectrophotometry

Specimens were obtained in heparinized (ammoniumheparinate) microhematocrit capillary tubes (Propper Manufacturing Co INC. Cat. No HCP). Plasma was separated in a hematocrit centrifuge. 0.050 ml of plasma was diluted with 0.800 ml distilled and deionized water. In order to eliminate interference, 0.100 ml of lanthanum solution was added. This was prepared by moistening 58.65 g La_2O_3 (Fluka AG Chemische Fabrik, puriss.) with water and adding 250 ml strong HCl (Merck, pro analyse) slowly until the substrate was completely dissolved. This was diluted to 1 000 ml distilled and deionized water. As control samples, lyophilisated control serums Monitrol I and II (Dade Division American Hospital Supply Corporation, Miami, Florida, USA) which had known concentrations of magnesium, were used. These concentrations were also checked by weight standards. Control and standard samples were handled in the same way as plasma samples. The calibration curve was linear in the relevant range. Specimens were stored at +4 C in a refrigator with the plasma separated. Determinations were done by duplicate measurements, twice a week, in series of 30—50 samples. Hemolytic samples were discarded. All Mg determinations were performed personally by M. Reinilä, M.Sc.

The apparatus was model 290 B Perkin Elmer atomic absorption spectrophotometer which had a burner planned by Boiling (Perkin Elmer part No 303-0202). The fuel was acetylene (pressure from bottle 0.8 kg/cm²). Adjustements fuel flow 14 and air flow 14. Suction was regulated so that the sample was aspirated at the rate of 1 ml/min to the burner. The lamp current was 2 mA, as informed

by the manufacturer Breadth of slit was 7 Å, and the magnesium absorption band at 2852 Å was used and was obtained with a coarse selection element 209.5 (7 38, 91 141 174 180)

The validity of micro samples of Mg was evaluated and the effect of possibly injured heels on Mg determinations was investigated. The analysis of the methodical error was also performed (See detailed reports in discussion.)

Serum calcium concentration was determined by complexometric titration method using EDTA solution and Cal-Red as indicator (18 127) Measurement of *serum phosphorus* was based on the molybdate method, phosphomolybdate complex being reduced by stannous chloride, the wavelength used in colorimetric determination was 625 mµ (76) *Blood glucose* concentration was measured with the glucose oxidase method (164), using the commercial reagent supplied by AB Kabi, Stockholm[1]

Statistical and mathematical analyses were carried out in the Computer Centre of the University of Oulu. Three levels of significance were used highly significant ($P \leq 0.001$)* * significant ($0.001 \leq P \leq 0.01$)** and almost significant ($0.01 < P \leq 0.05$)*

[1] Chemical analyses were performed in the laboratory of the Deaconess Institute, Oulu head M. Reinilä, M.Sc.

Results

1 MG CONCENTRATION OF VENOUS CORD BLOOD

22 plasma magnesium determinations of venous cord blood were performed The mean was 1 61 mEq/l ± SD 0.29 The mean Mg level of the first capillary samples of these 22 neonates was 1.83 ± 0.27 mEq/l. This was significantly higher than the cord blood concentration The study of the effect of perinatal stress on plasma magnesium is in progress (95)

2. RELATIONSHIP BETWEEN PLASMA [MG] AND GESTATIONAL AGE.

No significant correlation was found between gestational age and the mean Mg of the first day of life in the whole study population (the case of congenital nephrosis was excluded) Between gestational age and the mean Mg levels of the first two days a significant negative relationship was established (r = —0.26**) and there was a similar significant negative correlation between gestational age and the mean Mg level of the third to fifth days (r = —0.28**) No significant correlation between the mean Mg levels and gestational age was found on the fourth to fifth days.

A significant negative correlation was found between gastational age and the lowest Mg level reached during the first five days r = —0.28)

In order to find out the correlations of plasma Mg to gestational age and to birth weight, particularly in neonates who had no acid base disturbances the study patients were distributed into two groups according to whether they had abnormalities in the acid-base balance or not. Terminally ill infants, newborn babies of diabetic mothers and other infants suffering from marked acid-base disturbances were excluded from this *non-acid-base-disturbances group* This group of 81 infants was composed of 10 preterm neonates (less than 37 weeks of gestation) and 71 full term. There were 25 low birth weight infants (less than 2500 g) and 56 full birth weight infants in this group When the gestational age of this group was correlated with Mg levels, the following results were obtained. No significant correlation either with the mean Mg of the first day or of the first two days, but a significant negative correlation both with the mean Mg of the third to fifth, and of the fourth to fifth days (r = —0.28** and r = —0.32** respectively)

The group of infants not included in the non acid base disturbances group (one being the infant with congenital nephrosis) mostly had acidosis from the first to the second day Subsequently the acid-base status was usually normal or basic as a result of the treatment. When the mean Mg levels of this group consisting of 36 *newborn suffering from marked acid-base disturbances* (including terminally ill newborn and infants of diabetic mothers) were analyzed with regard to gestational age, the following correlations were established. Gestational age correlated with the mean Mg of the first postnatal day almost significantly negatively (r = —0.36*) and with the mean Mg of the first two days significantly negatively (r = —0.50**) The mean Mg of the third to fifth postnatal days did not show significant correlation with gestational age, nor did the mean Mg of the fourth to fifth days. This group comprised 20 preterm neonates (less than 37 weeks of gestation) and 16 full term. There were 19 low birth weight infants and 17 with birth weight ≥ 2 500 g

3 RELATIONSHIP BETWEEN PLASMA [MG] AND BIRTH WEIGHT

No significant correlation was found between birth weight and the mean Mg of the first postnatal day in the whole study population (the case of congenital nephrosis was excluded). Between birth weight and the mean Mg levels of the first two days, an almost significant negative correlation was established (r = —0.17*). Between birth weight and the mean Mg of the third to fifth days, a significant negative correlation was found (r = —0.32**). A highly significant negative correlation was found between birth weight and the mean Mg of the fourth to fifth days (r = —0.37***).

There was a highly significant negative correlation between birth weight and the lowest Mg level reached during the 5 days (r = —0.30).

When birth weight in the 81 newborn of the *non-acid-base-disturbances groups* was correlated with Mg levels, the following results were obtained. No significant correlation either with the mean Mg of the first day or first two days, a significant negative correlation with the third to fifth days (r = —0.32**) and a highly significant negative correlation with the mean Mg of the fourth to fifth days (r = —0.37***).

The group of 36 infants who had *marked acid-base disturbances* during the observation period of the first five days, was also analyzed with regard to the correlations of mean Mg levels with birth weight. No significant relationships were found between birth weight and mean Mg level either of the first postnatal day, of the first two days, or of the third to fifth postnatal days.

4 RELATIONSHIP BETWEEN PLASMA [MG] AND ACID-BASE BALANCE

In 66 neonates (34 low birth weight infants, 27 with gestational age less than 37 weeks) micro-Astrup was determined at the same time as magnesium determination or within 1 hour. The total number of such observations was 175. The infants of diabetic mothers excluded, a significant negative correlation between Mg and pH (140 observations) was revealed (r = —0.27**). Between Mg and standard bicarbonate a highly signifiant negative

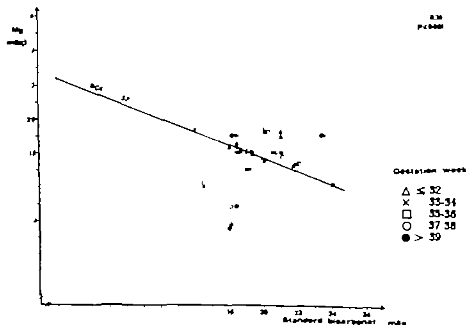


Fig. 2. Correlation of plasma Mg levels and blood standard bicarbonate in 57 newborns. Gestational ages in weeks are given in symbols.

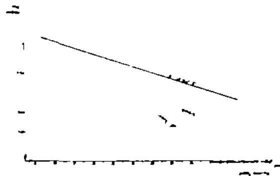


Fig 3. Correlations between plasma Mg and blood standard bicarbonate (— — —), between plasma Mg and blood pCO_2 ( ) and between plasma Mg and blood pH (———) in 7 terminally ill neonates. Correlation coefficients were respectively = —0,64 = —0.30* and = —0.47

correlation was observed (r = —0.36***) (Fig 2) Between Mg and pCO_2 no correlation was found (r = —0 10)

Between Mg and standard bicarbonate of the infants of diabetic mothers (35 observations) an almost significant negative correlation was found (r = —0.35) There was, however no significant correlation between the Mg and pH of infants of diabetic mothers (r = —0 16)

Six infants died during the observation period of the first five postnatal days, and one at the age of 11 days. One of them was the infant of a diabetic mother Towards the terminal phase Mg concentration of plasma showed a marked rise associated with metabolic acidosis, while in combined acidosis, and especially when a respiratory component was dominating, Mg level fell distinctly (Fig 3) Between Mg and pH (32 observations) a significant negative correlation was found (r = —0 47**) Terminally ill infants had a highly significant negative correlation between Mg and standard bicarbonate (r = —0.64**) An almost significant negative correlation was observed between pCO_2 and Mg (r = —0.30*)

pO_2 of arterial blood was determined 93 times at the same time as plasma [Mg] No correlation was found between these two factors (r = 0.12)

Plasma Mg levels of the non acid-base disturbances group of 81 neonates and those of the group of 36 infants who had marked acid-base disturbances are presented in Fig 4 (For definition of the groups, see page 22.) Except for the last value of 114 hours, Mg levels tended to be higher throughout the observation period in the group of infants with acid base disturbances. In the non acid base disturbance group there was an almost significant positive correlation between Mg levels and postnatal age (r = 0 63*) while in the acid base-disturbance group the correlation was not significant.

As can be seen in Fig 5 during the first 5 postnatal days the behaviour of plasma Mg levels showed a marked difference between preterm infants who had acid base disturbances and those who had not.

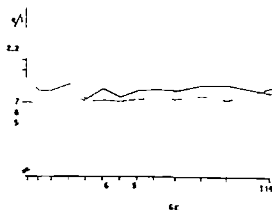


Fig 4 Plasma Mg levels of 36 neonates who had acid-base disturbances (———) and those of 81 neonates how had no acid-base disturbances (— — —) during the first 5 days of life.

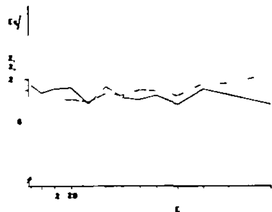


Fig 5. Plasma Mg levels of 20 preterm neonates (28—36) weeks who had acid-base disturbances (———), and those of 10 preterm neonates without acid-base disturbances (— — —) during the first 5 postnatal days.

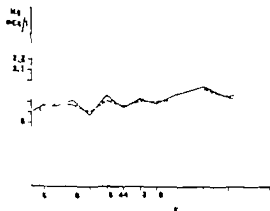


Fig. 6. Plasma Mg levels of low birth weight neonates (<2,500 g): 19 with (———) and 25 without (— — —) acid-base disturbances during the first 5 postnatal days.

On the first day the level had a tendency to be higher in the 20 infants with, than in the 10 without acid base disturbances, while from the third day on, plasma Mg was at a lower level in the acid base disturbance group the difference increasing towards the age of five days. In the preterms without acid base disturbances plasma Mg levels increased highly significantly with postnatal age (r = 0.90***) while in the preterms who had acid base disturbances there was an almost significant negative correlation between Mg level and postnatal age (r = —0.50*)

Whereas the plasma Mg concentrations in preterm and full term infants differed in behaviour the Mg in low birth weight and full birth weight neonates, on the contrary showed no such characteristic (see Fig 6) It was only at the age of 114 hours that the Mg level of the 19 newborn with marked acid base disturbances differed clearly from the corresponding value of the 25 low birth weight neonates who had no acid base disturbances. In the low birth weight infants without acid base disturbances plasma Mg increased significantly with postnatal age (r = 0.74**) and almost significantly in the group with acid base disturbances (r = 0.51*)

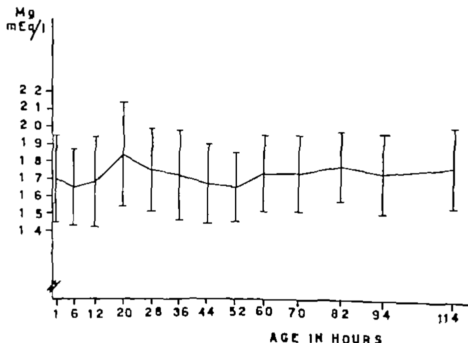


Fig. 7 Mean plasma Mg levels and standard deviations of 30 normal neonates during the first five day of life. A total of 322 observations were made.

5 PLASMA [MG] IN VARIOUS GROUPS OF NEONATES.

A total of 322 Mg determinations were performed on the plasma of 30 normal newborn infants who were considered *a normal control group* On an average, there were 10 7 observations per infant in this group

The behaviour of plasma [Mg] during the first 5 days in this group can be seen in Fig 7 (Table 4 in Appendix) The mean was lowest, 1 65 mEq/l, at the age of 2—8 and 48—56 hours, and highest, 1 84 mEq/l at the age of 16—24 hours. The gradual rise on the first day was almost significant (t = 1 811*) and the following decrease towards the age of 52 hours was significant (t = 2.803**) The Mg level showed a tendency to increase towards the end of the observation period, but the correlation of Mg with postnatal age was not significant (r = 1 700)

Twenty three infants had 1 min. Apgar scores below 6 Of these, *a postnatal asphyxia group* of nine had their plasma Mg determined at the age of 0—2 hours when the mean Mg level was 1.96 ± 0 28 This was significantly higher than the corresponding value for the infants whose 1 min. Apgar scores were 6—10 Six infants of the asphyxia group whose Mg levels had been determined at the age of 0—2 hours, had a gestational age of less than 37 weeks (one had 29 weeks and two 32 weeks) Four of them were infants of diabetic mothers. The birth weight of four infants of this group was below 2,500 g Among the 52 non-asphyctic infants (1 min Apgar 6—10) whose Mg levels had been determined at the age of 0—2 hours, there were 8 infants with a gestational age of less than 37 weeks and 14 newborn whose birth weight was below 2,500 g Two infants of diabetic mothers also belonged to the non asphyxia group Hypermagnesemia from postnatal asphyxia was no longer found at the age of 2—8 hours (Table 5)

When the plasma Mg values for 60 neonates aged 0—2 hours were correlated with the lowest Apgar scores, an almost significant negative relationship was found (r = —0.28*)

Twenty-one infants showed clinical signs of *intrauterine asphyxia*. Mg determinations were carried out on 10 of these infants at the age of 0—2 hours and showed a rather high mean Mg level for this group 1 88 ± 0 27 mEq/l This however did not deviate significantly from the corresponding value for 51 newborn who had no clinical signs of intrauterine asphyxia. (Table 5)

TABLE 5.

HYPERMAGNESEMIA RELATE TO ASPHYXIA.

Asphyxia group	Age	Number of observations	Mean mEq/l	SD	Compared with	Age	Number of observations	Mean mEq/l	SD	Difference¹ t-value
Postnatal asphyxia, 1 min Apgar ≤ 5	0—2 h	9	1.96	0.28	1 min Apgar 6—10	0—2 h	52	1 71	0.28	2.473
Intrauterine asphyxia	0 2 h	10	1.88	0.27	No signs of intrauterine asphyxia	0—2 h	51	1 72	0.29	1 609

¹ Student t-test

TABLE 6.

MAGNESIUM LEVELS [illegible] 9 [illegible] WHOSE [illegible] DIABETIC MOTHERS COMPARED[1] TO THE NORMAL CONTROL GROUP

Age	0—2 h	2—8 h	8—16 h	16—24 h	24—32 h	32—40 h	40—48 h	48—56 h	56—64 h	64—76 h	76—88 h	88—100 h	100—128 h
Mean mEq/l	2.13	1.88	2.12	1.98	1.89	1.85	1.82	1 77	1.82	1.59	1 72	1.87	1.69
SD	0.17	0.04	0.21	0.28	0.25	0.19	0.21	0.32	0.29	0.20	0.37	0.41	0.38
Number of observations	6	5	6	6	7	7	7	7	6	9	7	9	14

The material contained nine *infants of diabetic mothers* Five of the mothers were insulin dependent and one used oral therapy Two had gestational diabetes and one had latent diabetes. Five of them also had toxemia and two pyelitis. Six infants had postnatal asphyxia (1 min Apgar scores below 6) and two of them had signs of intrauterine asphyxia, as well. The mean birth weight was 3.5 kg and the mean gestational age was 36 weeks. One of the infants died at the age of five days. The group was rather small in number and there were rather few observations. When the mean Mg values of this group were compared with those of the normal control group significant hypermagnesemia was found during the first day See Table 6. Mg levels of this group showed a decreasing tendency with postnatal age ($r = -0.75^{**}$) The mean of 64—76 hours was almost significantly lower than the corresponding value of the normal control group ($t = 1.707$)

Nineteen mothers had had 1—2 *abortions* and three, 3 abortions. The mean plasma Mg levels of the newborn of these 22 mothers were higher than normal during the first day When 7 infants who belonged to other disorder groups were excluded 14 infants remained, whose mean Mg level was 1.89 ± 0.19 mEq/l at the age of 0—2 hours, which was almost significantly higher than normal ($P < 0.05$) The mean at 8—16 hours was 1.89 ± 0.24 mEq/l ($< P$ 0.05) (See Table 7) After the first day the mean plasma concentration decreased to the level of the normal control group. 10 mothers of this group were multiparous and five of them $\geq$ VI parous. Gestational age varied from 37 to 43 weeks. Four infants had postnatal asphyxia. The mean age of the mothers was 33 years, which was rather high. Maternal age, however had no correlation with Mg in the whole material ($r = -0.03$)

TABLE 7

ELEVATED PLASMA MAGNESIUM LEVELS IN 14 INFANTS WHOSE MOTHERS HAD HAD PREVIOUS ABORTIONS COMPARED[1] TO LEVELS IN THE NORMAL CONTROL GROUP

Age	0—2 h	2—8 h	8—16 h	16—24 h
Mean mEq/l	1.89*	1 73	1.89*	1.91
SD	0 19	0.42	0.24	0.21
Number of observations	7	4	11	8

Fourteen infants had a *gestational age of $\leq$ 34 weeks* and, after excluding one terminally ill infant and one born of a diabetic mother this group was compared to the normal control group It was found that the mean Mg was constantly elevated during the first days, the only exception being the value at 20 hours. The mean birth weight of these neonates was 1780 g, only three being small for date. (Table 8)

[1] Student t-test

TABLE 8.

HYPERMAGNESEMIA IN 12 NEONATES WITH GESTATIONAL AGE LESS THA 35 WEEKS

	Age 0—2 h	2—8 h	8—16 h	16—24 h	24—32 h	32—40 h	40—48 h	48—56 h	56—64 h	64—76 h	76—88 h	88—100 h	100—128 h
Mean mEq/l	2,08	1,90*	1,91	1,88	1,90*	1,96	1,89	1,99	1,89*	1,96	2,16	2,02	1,99*
SD	0,24	0,32	0,23	0,32	0,18	0,24	0,15	0,17	0,22	0,24	0,33	0,19	0,24
Number of observations	4	4	9	10	8	9	9	9	7	8	8	5	9

There were 10 *low birth weight infants of toxemic mothers* in the study population The mean plasma Mg level of this group was significantly lower than normal at 16—32 hours of age. The lowest mean Mg, 1 45 ±0 18 mEq/l, was at the age of 24—32 hours (see Table 9) All of these infants were small for dates. The mean birth weight was 2 100 g and the mean gestational age 38.5 weeks

The lowest mean Mg values were observed at the age of 56—128 hours in the highest *birth weight group of 4 050—4 620 g* The level was lowest, 1 40 ±0 14 mEq/l, at the age of 76—88 hours When the mean Mg levels of this group were compared with those of the normal con trol group it was found that the values at the age of 56 to 128 hours were con stantly significantly lower (Table 10) Gestational age of this group ranged from 36 to 42 weeks (mean 39.5) Two were neonates of diabetic mothers one had mild metabolic alkalosis at 80—100 hours of age.

TABLE 9

HYPOMAGNESEMIA IN 10 LOW IRTH WEIGHT NEONATES O TOXEMIC MOTHERS COMPARED[1] TO LEVELS IN THE NORMAL CONTROL GROUP

Age	16—24 h	24—32 h
Mean mEq/l	1.64	1 45
SD	0.25	0.18
Number of observations	9	8

The study population also contained one *infant with congenital nephrosis* From the very first determination and throughout the entire period of five days, the plasma Mg level was clearly higher than in other infants. Mg values ranged from 2.50 mEq/l to 2.65 mEq/l. In two micro-Astrup determinations the acid base ba lance was normal, while in one determi nation there was very mild metabolic acidosis.

TABLE 10.

HYPOMAGNESEMIA IN THE IRTH WEIGHT GROUP O 4050—4620 G (9 INFANTS) MEAN PLASMA MAGNESIUM ALUES COMPARED[1] TO THOSE O THE NORMAL CONTROL GROUP

	Age 56—64 h	64—76 h	76—88 h	88—100 h	100—128 h
Mean mEq/l	1.50*	1 46	1 40*	1 41	1 45
SD	0.11	0.18	0.14	0.14	0.15
Number of observations	7	12	5	12	4

Student t-test

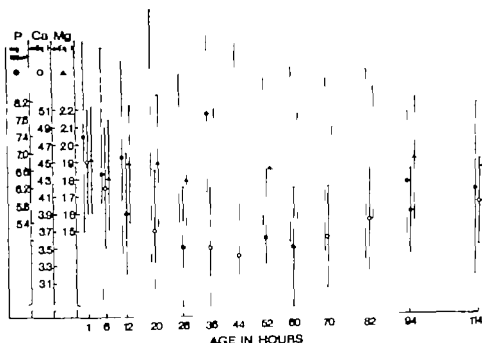


Fig 4. The behaviour of mean Mg, Ca and P and standard deviations during the first 5 postnatal days in 30 preterm neonates with gestational ages from 28—36 weeks.

Several factors *unrelated to significant deviations of plasma Mg levels* from those of the normal control group were detected in the study There were no sex differences. Small-for-date infants had no significant deviations from normal with the exception of the low birth weight infants of toxemic mothers. Maternal toxemia had no significant effect on plasma magnesium when birth weight was ≥ 2 500 g Infants with neurological symptoms, respiratory difficulties, hyperbilirubinemia and intra cerebral lesions tended to have slightly elevated mean Mg levels (1 80—1 81 mEq/l) but the deviations were not significant. The study's 9 cases of neonatal infections were not associated with hyper or hypomagnesemia. There were no significant differences between multiparity and primiparity The mode of delivery had no effect on plasma magnesium (Table 11)

TABLE 11

CLINICAL FACTORS UNRELATED TO SIGNIFICANT HYPER- OR HYPOMAGNESEMIA. THE MEANS OF 0—5 DAYS WERE COMPARED[1] TO THOSE OF THE NORMAL CONTROL GROUP. THE CASE OF CONGENITAL NEPHROSIS WAS EXCLUDED.

Factor	Mean mEq/l	Number of infants
Female	1 77 ±SD 0.31	38
Male	1 75 ±SD 0.29	62
Small for date	1 78 ±SD 0.30	41
Cesarean section	1 67 ±SD 0.26	26
Primiparity	1 76 ±SD 0.28	32
II—V—parity[2]	1 72 ±SD 0.31	56
Maternal toxemia, birth weight ≥ 2500 g	1 75 ±SD 0.26	18
Neurological symptoms	1.81 ±SD 0.25	31
Neonatal infections	1 71 ±SD 0.22	9
Other neonatal disorders[3]	1.80 ±SD 0.31	21

[1] Student t-test

[2] Group ≥ VI-parity of 10 infants contained 7 cases belonging to the hypermagnesemia groups, the rest were too few for analysis.

[3] Included respiratory disorders, hyperbilirubinemia, intracerebral lesions, congenital anomalies.

6 RELATIONSHIP BETWEEN CONCENTRATION OF PLASMA MAGNESIUM SERUM CALCIUM AND SERUM PHOSPHORUS

In preterm and term infants

Figure 8 presents the pattern of Mg Ca and P values at 13 average ages during the first five days of life in 30 infants with gestational ages from 28 to 36 weeks (Table 12 in Appendix)

The mean Mg varied within very narrow limits, the highest values 1 93 mEq/l at the age of 82 hours, being 8.5 per cent higher than the lowest values 1 78 mEq/l, at the age of 28 hours. (The difference was not significant) No significant correlation was found between Mg and postnatal age (r = 0 11)

In contrast to Mg, calcium fell distinctly being lowest, 3 4 mEq/l, at the average age of 44 hours. This value was 24 5 per cent lower than the highest value, 4 5 mEq/l at the age of 0—2 hours (P < 0 001)

After a small initial fall phosphorus showed a rising tendency up to 44 hours of age. Its maximal value was 7 9 mg/100 ml, which coincided with the minimum calcium levels. The maximal value of 7.9 mg/100 ml was 21.5 per cent higher than the value at the age of 6 hours. (P < 0 05) After the age of 44 hours, phosphorus fell distinctly

Figure 9 gives a pattern of the changes in magnesium, calcium and phosphorus at 13 average ages during the first five days of life in 87 infants with gestational ages from 37 to 44 weeks. (See Table 13 in Appendix)

The mean Mg levels changed little although a slight rising tendency could be found reaching the highest value of 1 79 mEq/l at the age of 114 hours, this value being 7 per cent higher than the lowest level, which was at the average age of six hours (P < 0 05) Age and Mg level showed an almost significant correlation during the five days (r = 0 51*)

In this group too, while Mg levels remained stable, calcium showed a clear fall, reaching the lowest value, 4 0 mEq/l, at 44 and again at 66 hours The fall was 15 per cent of the initial value of 4 7

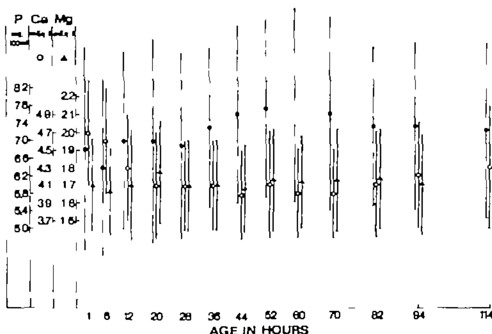


Fig 9. The behaviour of mean Mg, Ca and P and standard deviations during the first 5 postnatal days in 87 full-term neonates with gestational ages from 37—44 weeks.

mEq/l ($p < 0.001$) After reaching the lowest values, calcium tended to rise but rather slowly The level was, however higher than in preterm infants, throughout the observation period

After a slight initial fall, the mean of phosphorus showed a rising tendency reaching the highest value of 7 8 mg/100 ml at the average age of 60 hours. This was 22 per cent higher than the lowest value of 6 4 mg/100 ml at six hours ($P < 0.01$) The highest value for phosphorus coincided with the lowest for calcium. The lowest calcium value had however already been reached at the age of 44 hours, as well.

The difference in Mg levels of preterm and term infants was significant almost throughout the 5 days period, with exceptions at 6 h 16—32 h 70 h and 114 hours.

It was observed that in preterm infants with magnesium at a high level, calcium dropped 9.5 per cent units more during the first two days than in term infants, who had lower plasma Mg levels. There was no difference in the magnitude of increase of phosphorus levels during the first days in these groups, but in prematures the peak of phosphorus occurred approximately 16 hours earlier and was somewhat higher than in full-term infants.

In low birth weight infants and full birth weight infants

Fig 10 shows the behaviour of plasma magnesium, serum calcium and serum phosphorus in 44 low birth weight infants during the first five days distributed into 13 age groups. (Table 14 in Appendix.) The mean Mg showed a significant rising tendency towards the end of the observation ($r = 0.74$**) The maximal value was 1 93 mEq/l at 82 hours, which was 14 per cent higher than the lowest value of 1 69 mEq/l at the age of six hours ($P < 0.05$)

While Mg levels showed little variation, mean calcium fell from the initial value of 4 4 mEq/l to 3 7 mEq/l a fall of 16 per cent ($P < 0.001$)

Mean phosphorus showed a marked initial fall from 7 6 mg/100 ml to 6 1 mg/100 ml immediately after birth Then phosphorus rose to its maximal value of 7 6 mg/100 ml at 44 hours. The increase was 25 per cent ($P < 0.05$)

Fig 11 shows the mutual relationships between magnesium, calcium, and phosphorus in 73 neonates grouped together on the basis of birth weight (≥ 2 500 g) The values of 13 average age groups are given (Table 15 in Appendix.)

As in the former figures, it can be seen that magnesium levels were remarkably stable compared with the other two electrolytes. The lowest value of 1 68 mEq/l at 82 hours was 7 per cent lower than the highest 1 81 mEq/l, at the age of 20 hours (the difference was not significant) During the five days, the mean Mg in this group showed no significant change with age ($r = -0.22$)

Calcium fell from the initial level of 4.8 mEq/l to 3.9 mEq/l at 44 hours. This was a fall of 18 5 per cent ($P < 0.001$)

In this group phosphorus was not high immediately after birth the level was 6.7 mg/100 ml Phosphorus increased up to the age of 60 hours, reaching its maximal value of 7 9 mg/100 ml The rise was 18.5 per cent ($P < 0.01$)

It was found that, from the second to the fifth day magnesium in the low birth weight group was higher than in the full birth weight group a significant difference was found only at 60—100 hours. The fall of calcium during the first days was essentially of the same order of magnitude in the two groups. The increase of phosphorus was more rapid in the low birth weight group occurring about 12 hours earlier than in the full birth weight group but the levels of phosphorus were higher in full birth weight infants.

Generally it was observed that three facts coincided elevated magnesium, a pronounced fall in calcium and a rapid increase in phosphorus. When magnesium was in the order of 1 70 mEq/l there was a slower and less marked though significant, fall of calcium, and a slower but longer lasting increase of phosphorus. When the magnesium level was in the order of 1 80 mEq/l, as in low birth weight infants, the changes of calcium and phos-

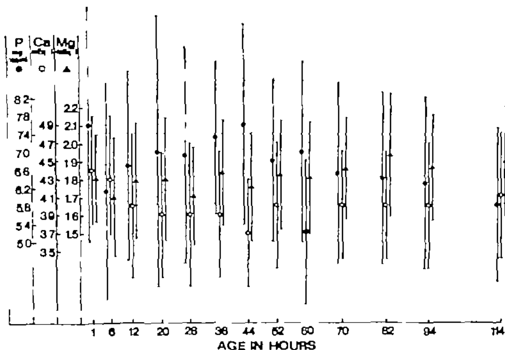


Fig 10 The behaviour of mean Mg, Ca and P and standard deviations during the first 5 postnatal days in 44 low birth weight neonates (<2,500 g)

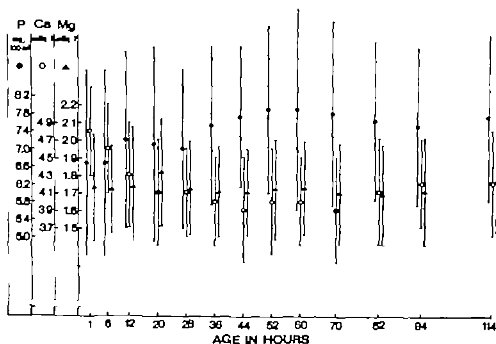


Fig 11 The behaviour of mean Mg, Ca and P and standard deviations during the first 5 postnatal days in 73 neonates whose birth weight was ≥ 2 500 g.

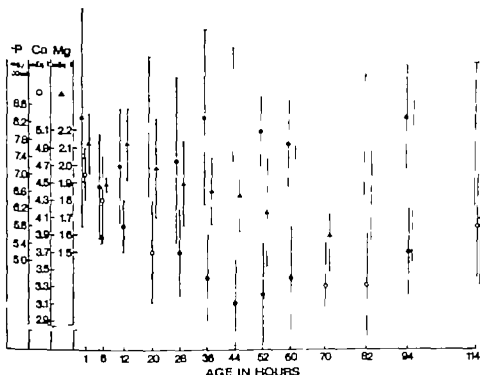


Fig 12. The behaviour of mean Mg, Ca and P and standard deviations during the first 5 postnatal days in 9 neonates of diabetic mothers.

phorus took place with intermediate speed and intensity

In infants of diabetic mothers

Fig 12 shows the changing pattern of magnesium, calcium and phosphorus values in 9 infants of diabetic mothers (Table 16 in Appendix.)

The behaviour of magnesium differed from that in the other groups. During the first day the level was abnormally high, averaging as much as 2.03 and the mean of the first two days, 1.95 mEq/l, was still elevated. From the third to the fifth day the level decreased to an average of 1 74 mEq/l. The lowest value was 1.59 mEq/l at 70 hours, which was 25.5 per cent less than the highest value at 0—2 hours. The fall was highly significant ($P < 0.001$)

The level of calcium showed an abrupt fall from the initial value of 4.6 mEq/l to 3 1 mEq/l at 44 hours a decrease of 33 per cent ($P < 0.001$) The lowest Ca values did not coincide with the lowest Mg values, although after 12 hours both showed a decreasing tendency and after 82 hours both tended to rise. Hypocalcemia in this group lasted from 36 to 82 hours, calcium level being throughout that time below 3.5 mEq/l. At 114 hours calcium rose to 4.0 mEq/l

Right from the start, phosphorus was at a high level. The initial value at 0—2 hours was 8.3 mg/100 ml, then there was a marked fall to 6 7 mg/100 ml and after that the peak value, 8 6 mg/100 ml, was reached at the age of 44 hours, which coincided with the most marked hypocalcemia. The increase was 28.5 per cent of the lowest value, reached at six hours ($P < 0.05$) Phosphorus showed only a slight decreasing tendency after its maximal value, remaining at the level of 7.9 mg/100 ml.

It could be found that in infants of diabetic mothers magnesium was more

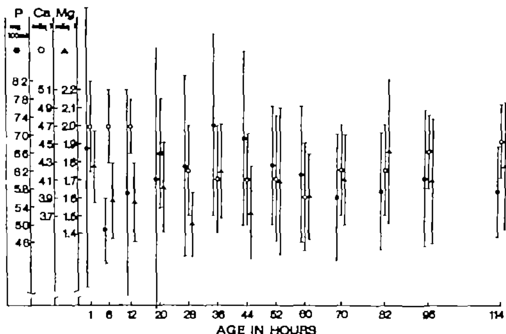


Fig 13. The behaviour of Mean Mg, Ca and P and standard deviations during the first 5 postnatal day in 10 low birth weight neonates of toxemic mothers.

elevated than in any other group during the first day calcium fell most abruptly and had the lowest values, and further phosphorus was higher than in any other group throughout the observation period

In low birth weight infants of toxemic mothers

Fig 13 shows the changes of magnesium, calcium, and phosphorus in 10 low birth weight infants of toxemic mothers during the five days of observation. (Table 17 in Appendix.)

It was demonstrated earlier in this study that there was significant hypomagnesemia in this group during the first and second day Magnesium showed considerable variations, the lowest level, 1 45 mEq/l, was reached at 28 hours, this being 20 per cent lower than the initial value of 1 77 mEq/l ($P < 0\ 01$)

The fall of calcium was not very marked in this group. Initially, Ca remained at the high level of 4 7 mEq/l for an abnormally long time, up to 12 hours subsequently falling at 60 hours, to the lowest value of 3.9 mEq/l, which was 17.5 per cent lower than the initial value ($P < 0\ 01$) After this minimum, the calcium level rose to 4.5 mEq/l by the end of the observation

Phosphorus showed a marked fall initially dropping from 6.7 mg/100 ml to 4 9 mg/100 ml. After that the level rose to the highest value of 7.2 mg/100 ml at the age of 36 hours. The increase was 46 per cent ($P < 0\ 05$)

In the neonate with congenital nephrosis

Not only magnesium, but also phosphorus showed a peculiar pattern of change in this infant. While the magnesium level was constantly high (ranges from 2.50 mEq/l to 2 65 mEq/l) phosphorus fell, after an initial value of 9.2 mg/100 ml, to very low levels. It reached the lowest value of 3.8 mg/100 ml at 54 hours and remained low on the fourth and fifth days, the level being 4 4 mg/100 ml at 126 hours.

Phosphorus differed entirely from the pattern found in other groups. The increase during the second and third days, that had been a characteristic of the other groups, was not found here

Calcium showed a typical fall after initial rather high values of 5 4—4.3 mEq/l, reaching its minimum of 3 4 mEq/l at 70 hours, a decrease of 37 per cent After that, calcium showed a rise similar to that in the majority of the study patients. The value at 126 hours was 4 6 mEq/l.

Correlations of plasma [Mg] with serum [Ca] and serum [P]

When the correlation of all the single values of Mg and Ca were calculated, a highly significant negative relationship was established (r = —0 19***) Between Mg and P an almost significant negative correlation was found (r = —0 05*)

In the group of neonates who had *no acid-base disturbances* (for definition of the groups, see page 22) a highly significant negative correlation was found between Mg and Ca (r = —0 19***) while an almost significant negative correlation was established between Mg and P (r = —0.05*)

In the group of newborn infants who had *marked acid-base disturbances* an almost significant negative correlation was found between magnesium and calcium (r = —0 13*) while a significant positive correlation was established between Mg and phosphorus (r = 0 15**)

In the *neonates of diabetic mothers* an almost significant positive correlation was found between Mg and Ca (r = 0.20*) while between Mg and P no significant correlation was established.

When 61 Mg values obtained at the age of 0—2 hours were correlated to the lowest calcium of the same patient, a significant negative relationship was established (r = —0.32**) (Fig. 14) Between the mean magnesium of the first day and the lowest calcium reached, a significant negative correlation was also found (r = —0.24 *) Between the mean Mg of the 4th to 5th days and the lowest calcium reached a significant negative correlation was again established (r = —0.31**)

In the group of neonates who had *no acid-base disturbances* there was no

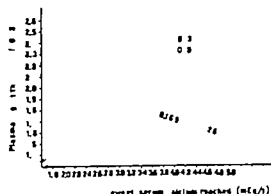


Fig 14 Correlation between plasma Mg 0—2 hours of age and the lowest serum Ca reached in 61 neonates.

significant correlation between either the mean Mg at 0—2 hours or that at 0—24 hours and the lowest calcium reached. Between the mean Mg of the 4th to 5th days and the lowest calcium reached, a significant negative correlation was found (r = —0.31 *)

In the group of neonates who had *marked acid-base disturbances* a significant negative correlation was established between the lowest calcium reached and the mean Mg at 0—2 hours (r = —0 62**) and again with that at 0—24 hours (r = —0.50**) while between the mean Mg of the 4th to 5th days and the lowest calcium reached, no significant correlation was found in this group

7 RELATIONSHIP BETWEEN PLASMA [MG] AND BLOOD GLUCOSE LEVELS

Except for a tendency to rise during the first day the levels of glucose showed no consistent behaviour in the different groups. The first values immediately after birth were the lowest. Mean values of glucose which could be considered as hypoglycemic were not found even in the neonates of diabetic mothers. Solitary hypoglycemic values were seen in the

study as well as cases of symptomatic hypoglycemia.

In neonates with a gestational age of 28—36 weeks the mean glucose level, 67 mg/100 ml, was higher than in neonates with 37—44 weeks of gestation, 54 mg/100 ml (the difference was not significant). Similarly the mean for low birth weight infants, 60 mg/100 ml, was higher than that for full birth weight infants, 57 mg/100 ml (the difference was not significant). See Table 18.

The correlation between Mg and glucose was analyzed: no significant correlations were found either in the neonates who had acid base disturbances, in neonates who had no acid base disturbances or in the newborn of diabetic mothers.

TABLE 18.

BLOOD GLUCOSE LEVELS IN GESTATIONAL AGE GROUPS AND BIRTH WEIGHT GROUPS.

	Age h 0—2	2—8	8—16	16—24	24—32	32—40	40—48	48—56	56—64	64—76	76—88	88—100	100—128
Gestational age 28—36 weeks													
Mean mg/100 ml	41	55	73	71	79	77	59	67	69	63	61	78	74
SD	32	28	59	42	54	77	30	40	36	32	28	65	34
Number of observations	23	23	30	29	28	28	29	28	28	28	27	25	24
Gestational age 37—44 weeks													
Mean mg/100 ml	40	50	44	55	51	55	54	57	63	57	59	63	61
SD	32	44	22	38	31	32	55	40	40	39	25	28	23
Number of observations	70	82	81	86	83	82	83	85	83	80	68	67	45
Birth weight < 2500 g													
Mean mg/100 ml	36	54	52	67	67	60	53	71	68	64	52	67	65
SD	21	51	34	48	46	53	23	56	40	57	17	56	29
Number of observations	32	32	41	43	41	42	40	41	39	40	37	33	30
Birth weight ≥ 2500 g													
Mean mg/100 ml	44	50	52	54	53	60	56	53	63	55	64	67	65
SD	37	31	40	33	34	46	60	25	38	18	29	32	27
Number of observations	61	49	70	72	70	68	70	72	71	68	58	59	39

Discussion

1 PATIENTS AND METHODS

Because the patients were selected, the study population does not represent a normal sample of newborn babies. When plotted against the chart of percentiles of intrauterine growth curves by Rantakallio (134) it can be seen that the distribution of the newborn is not even (see Fig 15.)

Gestational age was defined on the basis of the last menstrual period of the mother. Thus, being only an approximation, may give rise to error which could have a slight influence on the results.

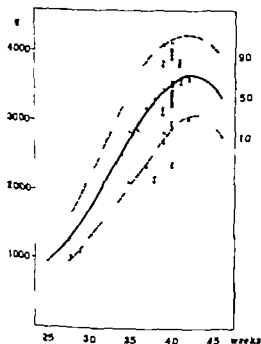


Fig 15. The study patients (130 neonates) plotted against the chart of percentiles of intrauterine growth curves (134).

Other clinical data concerning the maternal and neonatal history were highly reliable.

The total number of Mg observations was 1263, the density averaging 9.7 per infant. The lowest frequency of observations was in the terminally ill newborn (5.1). The major reason for a reduced number of observations was the poor condition of the infant, as in very small prematures. The failure to obtain as many Mg determinations immediately after birth as later was largely due to delay caused by resuscitative procedures and the transportion of the newborn infants to the neonatal unit.

It has been generally held, as stated by Anast (8), that every laboratory has its own standard for normal values of plasma magnesium, and the values have therefore differed. However, the great variations in the magnesium values reported (see Table 1) most likely reflect the different analytical methods used. Of direct colorimetry, the Titan yellow (improved modification) and Xylidylblue methods are accurate and are in current use. Haralambie and Keul did not find any difference between results obtained by Xylidylblue and by atomic absorption spectrometry in adults (82). Wacker, Iida, and Fuwa compared flame emission and atomic absorption spectrometry and they found no differencies in results (168). I have not found any reports of studies on the plasma of infants or children made by flame emission spectrometry. Improved fluorometry is in use and gives accurate results.

In atomic absorption spectrometry, the addition of lanthanum solution to diluted plasma sample aids in eliminating the interference of other ions. Accuracy, rapidity, reliability and availability for micro samples are the factors which have

made atomic absorption superior to any other analytical method for Mg determination at the present time.

Since Mg content of erythrocytes is about three times more than in the plasma (169) it is clear that hemolysis can markedly increase the plasma Mg concentration. That is why all hemolytic samples were carefully discarded. Hemolysis was estimated visually Evaporation was eliminated by storing samples in a refrigator

The validity of micro samples was evaluated by comparing them to the simultaneous venous samples in 11 neonates belonging to the normal control group. Micro determinations were slightly higher but the difference of these 25 paired observations was not significant (t= 0 84)

No significant error could be demonstrated to arise from the possible injury of heels punctured repeatedly This was checked by means of 7 simultaneous venous and capillary samples at the age of three to five days in neonates belonging to the normal control group Micro determinations tended to be higher but the difference was not significant (t = 1 68)

The analysis of the methodical error was performed by determining the plasma Mg concentration in 30 samples from the same (adult) person. This was carried out meticulously from the beginning to the end, by the same micro-method and by the same laboratory staff as were all the Mg determinations of the study The coefficient of variation of these 30 determinations was 2 11 % and thus the method can be considered highly reliable

In the present study standard deviation was generally in the same, or only slightly higher, class of magnitude as in normal adult humans studied by the atomic absorption method.

2. RELATION OF GESTATIONAL AND NEONATAL FACTORS TO PLASMA [MG]

Gestational factors

It was found in the present results that the mean plasma Mg concentration of the first 5 days was on a high level in neonates born before the 35th week of gestation. As shown by Aikawa and Bruns (4) in pregnant rabbits, magnesium rapidly crosses the placenta. In their study of the chemical composition of human fetus, Givens and Macy (71) found that the average content of Mg showed an increased utilization up to the 8th month the content per individual no longer showing an increasing tendency during the last two months of gestation Fee and Weil (50) showed that there was no consistent change of body Mg concentration with age or weight in stillborn or newborn infants dying at the latest at 10 days of age. Unlike the material of Givens and Macy the study patients of Fee and Weil did not include neonates with gestational age beyond 38 weeks.

Both the series referred to give evidence that the placental transfer of magnesium during the last two to three months of gestation differs from that of calcium. Givens and Macy stated that the greatest calcium deposition is made in the last three months of fetal life. A similar increase in Mg deposition could not to be found The results collected by Weil from the literature (175) give further support to this concept showing that magnesium in millimoles per kilogram (fat-free) tended to increase only slowly during gestation. It seems right to assume that the fetal magnesium concentration per body weight corresponding to near mature values is reached early during gestation. This agrees with the essential functions of Mg in cell metabolism.

Plasma magnesium concentration obviously does not reflect the total amount of body magnesium It would be pointless for the body content of Mg, one of the vitally important intracellular ions, to diminish towards maturity The inverse relationships between Mg and gestational age, and between Mg and birth weight observed in neonates in the present study most likely reflects a disturbed Mg homeostasis, an imbalance of factors regulating the intra and extracellular distribution of Mg and, in addition a deficiency of excretion of Mg via the kidneys.

It seems clear that during gestation the Mg intake is readily transferred from the mother via the placenta, to meet the

requirements of the fetal cells. The findings of early near mature values of fetal Mg concentrations supports this point of view. There is considerable evidence, based mainly on animal experiments, that the activity of the parathyroids is necessary for normal magnesium metabolism (10 29 45 63 66 67 104 126) Norris (123) and Scothorne (144) in their studies of human embryos and fetuses, came to the conclusion that the parathyroids are functioning during gestation.

Up till now the only conclusions to be drawn concerning the fetal plasma magnesium levels, have been based on determinations of the cord blood. The results of Salm (140) and Anast (8) are in agreement with the present findings of magnesium concentrations in cord blood, which were found to be significantly lower than the first values obtained postnatally. This possibly reflects the role of the placenta in the excretion of Mg during gestation.

Perinatal factors

Hyperosmolality observed immediately after birth and resulting from loss of water is more pronounced in preterm infants (59) and is probably an important factor contributing to elevated Mg levels during the first postnatal days. Perinatal stress, including increased tissue catabolism and decreased renal function together with fasting has been postulated to explain hyperosmolality (27)

In the present study hypermagnesemia at the age of 0—2 hours was found to be associated with birth asphyxia. The mean Mg of the first postnatal day was not significantly correlated with Apgar scores. Nor could the mean plasma Mg of the first day be demonstrated to correlate significantly with either gestational age or birth weight. In the present study the preterm newborn were more frequently asphyxiated than full term infants, since there was a significant positive correlation between 1 min. Apgar scores and gestational age and an almost significant correlation between 1 min. Apgar scores and birth weight. When there were signs of intrauterine asphyxia Mg level tended to be elevated, but the difference was not statistically significant when compared to the group of neonates who had no signs of intrauterine asphyxia. In asphyxia, verified both on the grounds of Apgar scores and of intrauterine indications, the obvious real cause of hypermagnesemia was fetal and or postnatal acidosis. The correlation of Apgar scores and the Mg values of 0—2 hours showed a significant negative relationship although this was not so statistically conclusive as in the study of Engel and Elin (47) In their series there was a negative correlation between cord blood Mg concentration and Apgar scores ($P < 0.001$) On the other hand in two other surveys (26 140) no correlation was found between Mg levels and birth asphyxia. Engel and Elin suggest that elevated plasma Mg levels may be evident only in series that include an appreciable number of severely depressed infants. Perhaps the technical disadvantages of earlier Mg studies have also obscured a possible correlation.

Connelly et al. (34) basing their conclusion on the rejection of phosphorus, found that the renal tubulus reacts only minimally to parathormone on the first day of life. The renal reactivity to exogenous parathyroid hormone increased markedly from the first to the third day of life. Connelly et al. concluded, from their study that neonatal hyperphosphatemia reflects not only a diminished parathormone responsiveness but also a secretory activity which is less than sufficient. Gardner et al. (58) showed that parathyroids of the newborn can respond to a high phosphorus load by increasing in volume, physiologic hypoparathyroidism resulting from the limitation in kidney function. This is not in disagreement with Norris (123) and Scothorne (144) who found histological and functional evidence of parathyroid activity during gestation. It seems likely that there are some factors functioning at birth or immediately thereafter which cause parathyroid suppression. One such factor could be hyperphosphatemia, as reported by many investigators (12, 58) Hypermagnesemia may possibly also contribute to depression of parathyroid activity Although information is lacking it is possible that this transient hypoparathyroidism, which may be mark

ed in premature infants, is connected with plasma Mg levels and with the occurance of hypermagnesemia in preterm infants.

Postnatal factors

Since the body and plasma concentrations of magnesium in adults are regulated mainly by the kidneys (88 149) it seems reasonable to suppose that the same is also the case with neonates. The kidneys of a newborn infant are not functioning fully and in prematures the renal insufficiency is accentuated Renal plasma flow in young infants is 20—50 per cent of adult values. Glomerular filtration rate in full term infants may be as low as 25 to 30 ml/min/1 73m² Values of small premature infants are generally lower and increase at a lower rate (Adults males 127 ml/min/1 73 m² females 117 ml/min/1 73 m²) Tubular reabsorption, as measured by glucose, is 60 mg/min/1 73 m² in the newborn (Adults males 364 females 303) (44) The pronounced quantitative incapacity of the operation of the kidneys in prematures is presumably the major explanation of the negative relationship found between the mean Mg of the third to fifth days and gestational age, and respectively between birth weight and the mean Mg of the third to fifth days and that of the fourth to fifth days. It is possible that while on the first day the most important factor affecting plasma Mg level is perinatal stress and especially acidosis, the most prominent factor from the second day on is impaired renal function.

Tsang and Oh (160) found in their study of low birth weight infants, (less than 2,000 g) an almost significant negative correlation between gestational age and the lowest serum Mg level reached during the first five days of life They found no significant correlation between birth weight and the lowest serum Mg level reached, although there appeared to be a trend towards lower values with increasing birth weight. In the present study when gestational age and birth weight were analyzed with regard to the lowest Mg levels of 0—5 days, a significant negative correlation was found between Mg and gestational age, and a highly significant correlation was established between Mg and birth weight. Tsang and Oh found the mean of their series to be 1 86 mEq/l, while in the present study the mean Mg of infants weighing less than 2,500 g ranged from 1 69 to 1,93 mEq/l. Żytkiewicz et al. reported the mean Mg of prematures on the second day of life as 1.34 mEq/l, ranges 0 83—1 71 mEq/l (183) and Harrison (83) 1 40 mEq/l ±0 08 These values are clearly lower than those of Tsang & Oh and of the present series.

Mean Mg levels of neonates with a birth weight of 2,500 g or more ranged from 1 68 to 1.81 mEq/l, and those of infants with a gestational age of 37—44 weeks were very close, 1 67—1 79 mEq/l. These two groups comprised mainly the same infants Mean Mg levels of the normal control group, which consisted of 30 normal neonates, ranged from 1 65 to 1 84 mEq/l. In each of these three groups magnesium averages show approximately similar patterns of change during the first five days. The rise discovered in term neonates at the age of 20 hours has not been observed in previous studies, in which samples have been taken at most, once a day This rise perhaps reflects the consequences of perinatal stress. The subsequent decrease during the second day may possibly result from the gradual removal of this effect. The rise in Mg levels found towards the age of five days probably reflects the cumulative effect of the impaired renal function on plasma Mg concentration. This increase was most marked in low birth weight infants. Tsang & Oh (160) made the same observation in their series of newborn weighing less than 2,000 g

Normal plasma Mg values during the first week of life reported in the literature are generally somewhat lower than in the present series. See Table 1 and 2 The average of Salmi (140) is higher 2 46 mEq/l, ranges 1.9—3.3 and that of Żytkiewicz et al (183) was 2.40 mEq/l, ranges 1 78—3 17 Obviously the most important reason for the great variations has been inaccuracy of analytical methods.

The adult values of normal plasma Mg studied by the atomic absorption method

are somewhat higher than the mean for full term infants in the present study Mean Mg levels in adults vary from 1 74 mEq/l to 2.14 mEq/l See Table 2

Birth asphyxia probably contributed to high Mg values at 0—2 hours of age in the infants of diabetic mothers, since six of them had 1 minute Apgar scores ≤ 5 and two of these had additional indica tions of intrauterine asphyxia. Compared with the asphyxia group, however the Mg level was higher at the age of 0—2 hours. In micro-Astrup determinations done immediately after birth, combined acidosis was usually observed. According to the Astrup findings, acidosis continued throughout the first day or long er in only three infants and was pre dominantly metabolic. Acid base balance often shifted to metabolic alkalosis, pre sumably because of the treatment and this was possibly connected with the low Mg levels observed on the third to fifth days. The mean Mg of the first day was 2 03 mEq/l, and the mean of the first two days was 1 95 mEq/l. These values were higher than normal. More marked perinatal stress than in other groups, together with postnatal acidosis and tissue catabolism, may be one reason for the hypermagnesemia in this group It is also possible that the tubular epithelium of infants born to diabetic mothers may have been more markedly underdeveloped, especially as the gestational age was usually less than normal.

Term infants of toxemic mothers show ed no deviations from the normal control group in their plasma Mg concentration. Toxemia, however obviously caused a disturbed placental transfer of Mg or an altered fetal Mg metabolism. Small for date infants of toxemic mothers in other words, those suffering from intrauterine malnutrition tended to have postnatal hypomagnesemia. The lowest mean Mg concentration was 1 45 ±0 18 mEq/l, which was very close to 1 46 mEq/l the mean of the corresponding group in the study of Tsang & Oh.

The lowest mean Mg values of the study were found in the birth weight group of 4 050—4 620 g, the lowest level 1 40 ±0 14 mEq/l, being at 76—88 hours of age No symptoms were associated with these values. The cause of low Mg values in the overweight newborn is obscure. The phenomenon may reflect the degree of maturity of the parathyroids and/or renal function in infants with a high birth weight. However the development of the kidneys correlates to gestational age rather than to birth weight and one would therefore have expected to find the lowest values in the highest gestation al age group although the development of renal and parathyroid maturity hardly occurs linearly in postmature neonates In the gestational age group of 41—44 weeks no hypomagnesemia was observed

The lowest value observed in the pre sent series was 1 00 mEq/l in three neonates, but no neurologic symptoms were noticed Tetany reported in hypomagnesemic states has generally been associated with Mg levels less than 1 00 mEq/l (6 128 139 181) Radde & al (132 a) have found signs and symptoms attributable to hypomagnesemia and/or hypocalcemia only if both calcium ion activity and magnesium were low In the present series, low total serum calcium was not coincident with the plasma Mg concentration of 1 00 mEq/l in any of the three neonates. In the present study the neurologic symptoms of 31 infants were not in even a single case associated with hypomagnesemia. In the group of neonates with neurologic symptoms, the mean Mg level did not deviate significantly from the normal control group The obvious cause in 15 symptom atic neonates was hypoglycemia, hypocalcemia in 4, central nervous system disease in 4 infection in 2 and miscellan eus in 6

There is no relevant explanation for the exceptionally high level of plasma Mg in the case of congenital nephrosis. The find ing possibly reflected placental insuffici ency anomalous renal function and other metabolic abnormalities, which were apparent immediately after birth (77) At the age of 11 months the Mg level of this patient was 1 82 mEq/l.

Neonatal infections and other disorders such as respiratory difficulties, hyperbilirubinemia and intracerebral lesions did

not cause changes in Mg levels unless they were associated with severe acid-base disturbances.

3 ACID-BASE DISTURBANCES AND PLASMA MAGNESIUM

The newborn maintain a lower pH and standard bicarbonate in the blood than do older subjects because of certain quantitative differences in the renal function. These differences are likely to be more pronounced in premature infants.

Blood pH, standard bicarbonate and pCO_2 were analyzed with regard to magnesium levels in the study There was an especially clear negative correlation between metabolic acidosis and Mg when infants of diabetic mothers were excluded. On the other hand, between respiratory acidosis and magnesium there was no correlation in the majority of the material. Most of the infants were in good condition and remained healthy throughout the whole observation period, and any respiratory acidosis was always treated promptly and effectively Thus in the whole group there were only a few patients suffering from serious respiratory acidosis.

Seven critically ill infants close to death had severe acid base disturbances. A negative correlation between pCO_2 and magnesium, observed in these infants, suggests that respiratory acidosis causes hypomagnesemia, while respiratory alkalosis leads to hypermagnesemia. Combined respiratory and metabolic acid base disturbances and the result of therapy make, however the interpretation of the correlation difficult. In addition, the number of observations, (32) is rather small for reliable conclusions to be made. Further investigations are needed

In atomic absorption spectrophotometry the interference of other ions is eliminated. Therefore the reason for hypermagnesemia in metabolic acidosis cannot be technical In metabolic acidosis magnesium and potassium have been shown to move out of cells into the plasma (155) Whang & Wagner occluded venous blood flow from the exercising arm and observed rising plasma Mg K and hemoglobin concentrations and decreasing blood pH (176) They think that the changes in plasma Mg concentration most probably reflect the movement of water into the cells. In the study of Engel & Elin (47) the hemoglobin concentrations increased significantly during asphyxia but there was no increase of sodium and calcium concentrations. Thus it is obvious that a shift of extracellular water into cells is not the sole explanation of the hypermagnesemia following birth asphyxia. On the other hand a low pH has been observed to cause a decrease in muscle magnesium concentrations *in vitro* (62) This provides suggestive evidence for the displacement of magnesium from the intracellular phase to extracellular fluid in acidosis. Further evidence for this is the raised serum Mg concentration found in uncontrolled diabetes (30 119)

Hypermagnesemia associated with metabolic acidosis occurred in term infants as well as in preterms but, as can be seen in Fig 2 the highest values with metabolic acidosis were seen in those born before term. This can perhaps be partly explained by the fact that the response of the kidneys to acidosis is apparently not so good in preterm as in term infants. In the present study however the lowest measured standard bicarbonate did not correlate significantly with gestational age or birth weight Hypermagnesemia in metabolic acidosis may possibly reflect an attempt of the organism to buffer acidosis with magnesium ions, a phenomenon found to be associated with other ions in chronic acidotic states (100 155)

The differences found in Mg levels during the 5 postnatal days in the newborn with, and without acid base disturbances indicate that plasma Mg levels show an increasing tendency towards the age of 5 days if there is no acid base disturbance. The treatment of postnatal acidosis with sodium bicarbonate probably caused the decrease from the Mg levels of the first day to the clearly lower values observed from the third to fifth days of age. This was most distinctly found in the preterm infants.

Relations with calcium and phosphorus

Magnesium and calcium metabolism show marked similarities. Both are divalent ions and a decrease in the serum level of either is associated with an increase in neuromuscular irritability. It has been shown in animal experiments that there is a common reabsorptive path for calcium and magnesium both in the gut and in the renal tubule. Phosphate infusion in dogs results in decreased serum levels of calcium and magnesium (101). Phosphate further influences the intestinal absorption of Mg and Ca (6, 33). Vitamin D has an effect on the absorption of both the Mg and the Ca in the gut (80, 112, 113). Bone is the chief reservoir for both ions.

The parathyroid hormone exerts an influence on calcium, phosphorus and magnesium metabolism, and thus these ions are all interrelated. In the present series it was found that the higher the plasma Mg level, the lower was the lowest calcium value on the second to third day. In preterm groups the fall of calcium between the 24th and 64th hours was more marked than in term infants. The corresponding increase in phosphorus levels showed no such characteristic patterns in different gestational age and birth weight groups. The relationship between Mg and Ca P homeostasis is not wholly understood (122). Neonatal hypocalcemia and hyperphosphatemia are thought to be due to functional hypoparathyroidism and/or renal immaturity (34, 58).

The correlations found between the lowest calcium reached and the mean Mg of various postnatal ages in groups of neonates with, and those without acid base disturbances suggest that in neonates with acid-base disorders (mainly acidosis) hypermagnesemia on the first postnatal day is associated with hypocalcemia during the second to third days. The observation of a significant negative correlation between the lowest Ca reached and the mean Mg of the 4th to 5th postnatal days in neonates without acid-base disturbances, pr[illegible] uggestive evidence of the roi[illegible] insufficient renal function as one rea[illegible] this inverse relationship. This i[illegible] support d by the elevated Mg levels observed in renal insufficiency in adults (118, 166).

Bergman suggested skeletal mineralisation or a thyrocalcitonin response as a hypothesis for neonatal hypocalcemia (17). Radde & al. (132 a) observed that acute hypermagnesemia in the rat led to transient hypercalcemia. This effect was not seen in animals in whom the thyroid glands had been removed, but was present if parathyroidectomy alone had been carried out. In *in vitro* incubation studies, they confirmed that an excess of Mg ions led to discharge of calcitonin from c-cells. However, Mg concentrations had to be increased by 100 % before measurable changes in hormonal release could be detected, whereas parallel experiments with varying calcium concentrations in the medium showed that a 20 % increase in [Ca] was sufficent to produce measurable calcitonin release. Thus they concluded that increase in Mg levels produces release of calcitonin only under exceptional circumstances, as might be the case in chronic renal failure. Although no information concerning calcitonin concentrations or function in the newborn period is available, it may be hypothesized that the elevated Mg levels seen in the neonates of diabetic mothers and in preterm infants could stimulate calcitonin secretion, which in turn could contribute to the development of hypocalcemia during the first two days.

In their study of neonatal hypocalcemia in low birth weight infants, Tsang & Oh discovered that these infants, prior to becoming hypocalcemic, had a significantly lower pH at 8 hours of age than non-hypocalcemic infants (159). In the present study an inverse relation was observed between Mg and pH and especially between Mg and standard bicarbonate. There may be some connection between hypermagnesemia and metabolic acidosis and the later occurence of hypocalcemia.

A high Mg level coinciding with a pronounced fall in calcium and rapid

increase in phosphorus was most clearly demonstrated in the infants of diabetic mothers. It has been verified in many investigations that maternal diabetes or prediabetes is a predisposing factor to neonatal hypocalcemia (68 69 116) In the present study the Ca level in infants of diabetic mothers was below 3.5 mEq/l from the average age of 36 hours to 82 hours. These findings obviously suggest that parathyroid and renal immaturity were more marked in neonates of diabetic mothers, and this possibly was also the major factor in the elevation of the Mg level. The Mg Ca and phosphorus behaviour in this group closely parallelled that observed by Gardner & al. (58) in a newborn baby under a condition of a dietary phosphate load and under a calcium load. They found a fall of both serum Mg and Ca to low levels coincident with a rise of serum phosphorus to maximal levels. In the infants of diabetic mothers the behaviour of Mg resembled that of Ca only the change was slower and less intensive The positive correlation between Mg and Ca in this group was possibly the result of an endogenous phosphorus load In the case observed by Gardner & al. a dietary calcium load added to a phosphate load was associated with the rise to a normal level of serum Mg and Ca. The metabolic balance studies suggested that disturbances of the dietary Ca Mg ratio resulted in an internal redistribution of magnesium

In several reports hypocalcemia has been shown to coexist with hypomagnesemia in infants (56 70, 128, 139) Moreover in the study of Gittleman & al. (70) a significant positive correlation was found between the mean calcium and magnesium levels in the full term hypocalcemic infants, while Tsang & Oh did not find a significant correlation between Mg and Ca levels in low birth weight infants (160) In the present series an almost significant positive correlation was found between Mg and Ca in the infants of diabetic mothers, while a highly significant negative correlation was observed in the whole study population This finding agrees with that of Gittleman & al., since the infants of diabetic mothers were mostly hypocalcemic, and it possibly reflects the similar metabolic handling of the two ions in hypocalcemia.

Some reports have related high phosphorus levels to both low calcium and low magnesium levels (58) Tsang & Oh (160) did not find any significant correlation between Mg and phosphorus. In the present study an almost significant negative correlation was found between Mg and phosphorus in the whole study population. The present results further reveal that phosphorus has an increasing tendency with birth weight and gestational age, while the reverse was true of magnesium. This gives suggestive evidence of the depressive effect of phosphorus on magnesium levels. This interaction, paralleling that between Ca and phosphorus, may possibly reflect skeletal mineralisation. Hypoparathyroidism induced by high phosphorus would be one possible explanation for the inverse relation between Mg and P

The significant positive correlation found between Mg and P in the newborn who suffered from marked acid base disturbances, possibly reflects the simultaneous release of these intracellular ions out of cells in tissue anoxia and catabolism.

The inverse relationship found between magnesium and calcium suggests that, e.g in preterm infants with low or moderate mean phosphorus levels, the role of hypermagnesemia, possibly combined with that of phosphorus, may be of some importance in the depression of calcium levels. These findings obviously reflect a change in the homeostatic relations between Mg Ca, and P with increasing gestational age and birth weight, as well as in some disorder conditions.

In the study of Tsang & Oh (159) hypocalcemia was noticed significantly more often in infants whose mothers had had previous abortions. In the present study hypermagnesemia during the first day was observed in the infants of mothers who had had abortions. In this group no hypocalcemia was found. Recidive abortions may reflect some disorder of pregnancy and possibly the first-day hypermagnesemia was an indication of such a disorder In addition, the maternal age

of this group was rather high. The neonates of this group appeared well and normal, four had mild postnatal asphyxia.

Relation with blood glucose

The present results reveal that magnesium and glucose do not show significant correlations during the early newborn period. It has been shown in animal experiments (2, 86) that magnesium metabolism is intimately related to that of carbohydrate. Aikawa (9) found in rabbits, that after an injection of Mg^{28} and glucose, there was an increase in the tissue magnesium content of the heart and muscle coincident with a significantly increased blood glucose level, and also a slight increase in serum Mg. In the present series, blood glucose concentration was somewhat, but not significantly, higher in preterm than in term infants. A similar but even smaller difference was found between low birth weight and full birth weight infants. This difference was possibly the result of therapy since according to several investigations (36, 133) premature infants tend to have lower blood glucose levels as compared to mature newborns.

Summary

The aim of the investigation was to elucidate magnesium metabolism during the first few days of life by studying the pattern of the plasma Mg levels.

The study comprised an analysis of 1263 serial magnesium determinations performed by atomic absorption spectrophotometry on the plasma of 130 neonates in the first five days of life 30 of them constituted a normal control group. Gestational age varied from 28 to 44 weeks, and birth weight from 1020 g to 4620 g The study population included groups of infants with various neonatal disorders. Serum calcium, phosphorus and blood glucose levels were determined at the same time as magnesium Two to three samples were obtained for each of the first three days, on the fourth day two samples and on the fifth day one.

Plasma magnesium levels were correlated to gestational age and birth weight. The behaviour of plasma Mg in various neonatal disorders was investigated. The relations of plasma Mg to serum calcium, phosphorus and blood glucose were analyzed

1 A significant negative correlation was established between the mean Mg of the 3rd to 5th days and both gestational age and birth weight in the whole study population. The mean Mg of the first day did not show a significant correlation with gestational age or birth weight. The correlations of gestational age and birth weight with plasma [Mg] at various postnatal ages differed whether neonates had acid base disturbances or not. In the newborn without acid base disturbances, a significant negative correlation was found between the mean Mg of the 4th to 5th postnatal days and both gestational age and birth weight while in the newborn with acid-base disturbances (acidosis from the first to the second day) a significant negative correlation was established between gestational age and the mean Mg of the first two days, but not with that of later postnatal ages. In this group no significant correlations were found between birth weight and plasma Mg levels.

The established correlations suggest that high plasma Mg levels on the first day reflect perinatal stress, especially acidosis, and Mg levels at 3 to 5 days of age mainly reflect the immaturity of the renal and hormonal control of magnesium metabolism. This was more pronounced in premature infants.

Magnesium concentration of venous cord blood was significantly lower than the mean of the first capillary samples in 22 neonates.

2. The group of 30 normal neonates showed an almost significant increase of Mg level on the first day and a significant decrease subsequently towards the third postnatal day The level tended to increase during the first five days, although not significantly The mean Mg of this group ranged from 1 65 mEq/l to 1 84 mEq/l.

Hypermagnesemia at 0—2 hours of age was observed in the newborn with birth asphyxia when compared to those without asphyxia. Hypermagnesemia was no longer found at the age of six hours. An almost significant negative correlation was established between the lowest Apgar scores and the Mg values of 0—2 hours of age. In 66 neonates, acid base balance determined by micro-Astrup method was performed coincident with plasma magnesium determination Plasma Mg levels were found to have a highly significant

negative correlation with standard bicarbonate. These findings are in accordance with previous observations.

Various groups of neonates who had abnormalities in the maternal or gestational history or in the perinatal or postnatal course, were analyzed with regard to deviations of plasma Mg levels by comparing them to the normal control group. Hypermagnesemia was found in the following groups

a) in neonates with gestational age less than 35 weeks, throughout the first 5 days,
b) in neonates of diabetic mothers, on the first day
c) in neonates of mothers who had had previous abortions, on the first day

Hypomagnesemia was found
a) in low birth weight neonates of toxemic mothers, at 16—32 hours of age
b) in neonates with birth weight of 4050—4620 g, at 56—128 hours of age.

3 In the study it was found that there was a highly significant negative correlation between plasma [Mg] and serum [Ca] and an almost significant negative correlation between plasma [Mg] and serum [P] in the whole population.

In the neonates who had marked acid base disturbances a significant positive correlation was established between Mg and P This possibly reflects the release of intracellular Mg and P in tissue anoxia and catabolism

Unlike the other groups, the neonates of diabetic mothers showed an almost significant positive correlation between Mg and Ca. This possibly reflects the effect of a high phosphorus content on both the Mg and the Ca in this group The behaviour of Mg somewhat resembled that of calcium in this group

In the whole study population a significant negative correlation was established between the lowest serum [Ca] reached and the plasma [Mg] at 0—2 hours of age, between the lowest Ca and the mean Mg of the first day and between the lowest Ca and the mean Mg of the 4th to 5th days.

The correlation between the Mg levels and the lowest Ca differed according to whether or not the newborn had acid base disturbances. In the neonates who had no acid-base disturbances, there was no significant correlation between the lowest Ca reached and either the Mg of 0—2 hours of age or the mean Mg of 0—24 hours. Between the mean Mg of the 4th to 5th days and the lowest Ca reached, a significant negative correlation was found. In the neonates who had marked acid base disturbances, there were significant negative correlations between the lowest Ca and both the Mg of 0—2 hours and the mean Mg of 0—24 hours. However the mean Mg of the 4th to 5th days and the lowest Ca value showed no significant correlation.

These correlations can be interpreted as a reflection, on the one hand, of the effect of perinatal factors on Mg, Ca and P and, on the other hand, as a manifestation of immature renal and hormonal function.

In conclusion, the present results cast some light onto the role of magnesium in the mineral metabolism of the newborn. They suggest the intimate relationships between Mg, Ca and P The results possibly also present some new aspects of the birth mechanism of »first-day» hypocalcemia

Summary

The aim of the investigation was to elucidate magnesium metabolism during the first few days of life by studying the pattern of the plasma Mg levels.

The study comprised an analysis of 1263 serial magnesium determinations performed by atomic absorption spectrophotometry on the plasma of 130 neonates in the first five days of life 30 of them constituted a normal control group Gestational age varied from 28 to 44 weeks, and birth weight from 1020 g to 4620 g The study population included groups of infants with various neonatal disorders. Serum calcium, phosphorus and blood glucose levels were determined at the same time as magnesium. Two to three samples were obtained for each of the first three days, on the fourth day two samples and on the fifth day one.

Plasma magnesium levels were correlated to gestational age and birth weight. The behaviour of plasma Mg in various neonatal disorders was investigated. The relations of plasma Mg to serum calcium, phosphorus and blood glucose were analyzed.

1 A significant negative correlation was established between the mean Mg of the 3rd to 5th days and both gestational age and birth weight in the whole study population. The mean Mg of the first day did not show a significant correlation with gestational age or birth weight. The correlations of gestational age and birth weight with plasma [Mg] at various postnatal ages differed whether neonates had acid-base disturbances or not. In the newborn without acid-base disturbances, a significant negative correlation was found between the mean Mg of the 4th to 5th postnatal days and both gestational age and birth weight while in the newborn with acid-base disturbances (acidosis from the first to the second day) a significant negative correlation was established between gestational age and the mean Mg of the first two days, but not with that of later postnatal ages. In this group no significant correlations were found between birth weight and plasma Mg levels.

The established correlations suggest that high plasma Mg levels on the first day reflect perinatal stress, especially acidosis, and Mg levels at 3 to 5 days of age mainly reflect the immaturity of the renal and hormonal control of magnesium metabolism. This was more pronounced in premature infants.

Magnesium concentration of venous cord blood was significantly lower than the mean of the first capillary samples in 22 neonates.

2. The group of 30 normal neonates showed an almost significant increase of Mg level on the first day and a significant decrease subsequently towards the third postnatal day The level tended to increase during the first five days, although not significantly The mean Mg of this group ranged from 1 65 mEq/l to 1 84 mEq/l.

Hypermagnesemia at 0—2 hours of age was observed in the newborn with birth asphyxia when compared to those without asphyxia. Hypermagnesemia was no longer found at the age of six hours. An almost significant negative correlation was established between the lowest Apgar scores and the Mg values of 0—2 hours of age. In 66 neonates, acid base balance determined by micro-Astrup method was performed coincident with plasma magnesium determination. Plasma Mg levels were found to have a highly significant

sogy 20 133, 1966.

142. SA AGE, D. C. L. & MCADAM, W A. F: Convulsions due to hypomagnesaemia i infant recovering from diarrhoea. *Lancet, 2* 234, 1967

143. SCHACHTER, D.: The fluorometric estimation of magnesium in serum and urine. *J Lab Clin Med, 54* 763, 1959.

144 SCOTHORNE, R. J Functional capacity of fetal parathyroid glands with referenc to their clinical use as homografts. *Ann N Y Acad Sci, 120:* 669 1964.

145. SEELIG, M. S. Requirements of magnesium by normal adult summary and analysis of published data. *Amer J Clin Nutr 14* 242, 1964

146. SIGGAARD-ANDERSEN, O., ENGEL, K., JORGENSEN, K. & ASTRUP P: A micromethod for determination of pH CO tension, base excess and standard bicarbonate in capillary blood. *Scan J Clin Lab Invest, 12* 172, 1960.

147 SINCLAIR, J G: Size of parathyroid glands of albino rats as affected by pregnancy and controlled diets. *Anat Rec, 80* 479, 1941

148. SMITH, W O & HAMMERSTEN, J F: Serum magnesium in renal diseases. *Arch Int Med, 102* 5, 1958.

149. STEWART C. P & FRAZER, S. C. Magnesium. In H. Sobotka & C. P Stewart (eds.) *Advances in Clinical Chemistry* Academic Press, New York 1963, vol. 6, p. 29

150. STEWART W F HUTCHINSON, F & FLEMING, L. The estimation of magnesium in serum and urine by atomic bsorption spectrophotometry *J Lab Clin Med, 61* 858, 1963.

151 STUTZMAN, F L. & AMATUZIO, D. S. A study of serum and spinal fluid calcium and magne ium in normal humans. *Arch Biochem, 39* 271 1952.

152. TAITZ, L. S., ZARATE-SALVADOR, C. & SCHWARTZ, E. Congenital absence of the parathyroid and thymus glands in an infant (III and IV pharyngeal pouch syndrome) *Pediatrics, 38* 412, 1966.

153. TAN, Y F Total and ultrafiltrable serum magnesium and calcium in normal children and adults in Singapore. *J Singapore Paediat Soc, 10* 115, 1968.

154. TEISSIER, G. La relation d'allometrie. Sa signification statistique et biologique. *Biometrics, 4* 14 1948.

155. THORÉN L. *Vätskebalans en översikt för klinisk bruk.* Almqvist & Wiksell, Stockholm, 1969, 4th ed. p. 59

156. TIBBETTS, D M & AUB, J C Magnesium metabolism in health and disease. I The Mg and Ca excretion of normal individuals, also the effects of magnesium, chloride and phosphate ions. *J Clin Invest 16* 491 1937

157 TISSIERES, A. & WATSON, J D Ribonucleoprotein particles from *Escherichia coli. Nature (London) 182* 778, 1958.

158. TISSIERES, A., WATSON, J D SCHLESSINGER, D & HOLLINGWORTH, R B Ribonucleoprotein particles from *Escherichia coli. J Molec Biol, 1* 221 1959

159 TSANG, R. C. & OH, W Neonatal hypocalcemia in low birth weight infants *Pediatrics, 45.* 773, 1970

160. TSANG, R. C. & OH W: Serum magnesium levels in low birth weight infants. *Amer J Dis Child, 120* 44 1970.

161 TS'O, P O. P., BONNER, J & VINOGRAD, J Microsomal nucleoprotein particles from pea seedlings. *J Biophys Biochem Cytol, 2* 451 1956.

162. VALLEE, B. L., WACKER, W E. C. & ULMER, D. D Magnesium deficiency tetany syndrome in man. *New Eng J Med, 262* 155, 1960.

163. VENNER, H. & ZIMMER, C. Studies on nucleic acids. VIII Changes in stability of DNA secondary structure by interaction with divalent metal ions. *Biopolymers, 4* 321 1966.

164 DE VERDIER, C-H. HJELM, M. LINDE, S. LUNDÉN, R & WESTLUND, L. E. Glykosbestemming i blod med hjalp glykosoxidas. *Nordisk Med, 71* 392 1964

165 VITALE, J J NAKAMURA, M. & HEGSTED, D. M. Effect of magnesium deficiency on oxidative phosphorylation. *J Biol Chem, 228* 573 1957

166. WACKER, W E. C. & VALLEE, B. L. Study of magnesium metabolism in acute renal failure employing multichannel flame spectrometer *New Eng J Med, 257* 1254, 1957

167 WACKER, W E. C. MOORE, F D., ULMER, D D. & VALLEE, B. L. Normocalcemic magnesium deficiency tetany *J A M A, 180* 161 1962.

168. WACKER, W E. C., IIDA, C. & FUWA, K. Accuracy of determinations of serum magnesium by flame emission and atomic absorption spectrometry *Nature (London) 202* 659, 1964

169. WACKER, W E. C. & PARISI, A. F Magnesium metabolism. *New Eng J Med, 278* 658, 712, 772, 1968.

170. WALLACH, S. CAHILL, L. N. ROGAN, F H. & JONES, H. L. Plasma and erythrocyt magnesium in health and disease. *J Lab Clin Med, 59* 195, 1962.

171 WALSER, M Ion association. VI. Interactions bet een calcium, magnesium, inorganic phosphate, citrate and protein in normal human plasma. *J Clin Invest, 40* 723 1961

172. WALSER, M. Separate effects of hyperparathyroidism, hypercalcemia of malignancy renal failure, and acidosis on state of calcium, phosphate and other ions in plasma. *J Clin Invest, 41* 1454 1962.

173. WALSER, M. Magnesium metabolism. *Ergebn Physiol, 59* 185, 1967

174 WALSH, A. The pplication of tomic absorption spectra to chemical analysis. *Spectrochim Acta, 7* 108, 1955.

175. WEIL, W B. J Chemical composi ion of the fetus. I H I Barnett (ed.) *Pediatrics,* Butterworths, London, Appleton-Century-Crofts, Division of Meredith Corporation, New York 1968, p. 1330.

176. WHANG, R. & WAGNER, R. The influence of venous occlusion and exercise on serum magnesium concentration. *Metabolism, 15* 608, 1966.

177 WIDDOWSON, E. M. Metabolic effects of fasting and food. I G E. W Wolstenholme & M. O Connor (eds.) *Ciba Foundation Symposium on Somatic Stability in the Newly Born.* J A. Churchill, Ltd. London 1961.

178. WIDDOWSON, E. M., MCCANCE, R. A. & SPRAY C. M. Chemical composition of human body *Clin Sci*, *10* 113, 1951
179. WIDDOWSON, E. M. & MCCANCE, R. A. The metabolism of calcium, phosphorus, magnesium and strontium. *Pediat Clin N Amer* *12* 595, 1965.
180. WILLIS, J B. The determination of metals in blood serum by atomic absorption spectroscopy II. Magnesium. *Spectrochim Acta*, *16* 273, 1960.
181 WONG, H. B. & TEH, Y F: An association between serum-magnesium and tremor and convulsions in infants and children. *Lancet*, *2* 18, 1968.
182. WORKER, N A. & MIGICOVSKY B. B. Effect of vitamin D on utilization of beryllium, magnesium, calcium, strontium and barium in chick. *J Nutr* *74* 490, 1961
183. ŻYTKIEWICZ, A., BARTOSZEWSKI, A., MODZELEWSKA, L. & WARBIAKOWSKI, H. Poziom magnezu w surowicy krwi noworodków i ich matek. *Polski Tyg Lek*, *20* 1316, 1965.

Appendix

TABLE 4.

PLASMA MAGNESIUM LEVELS IN THE NORMAL CONTROL GROUP (30 NEONATES)

	Age 0— 2 h	— 8 h	8— 16 h	16— 24 h	24— 32 h	32— 40 h	40— 48 h	48— 56 h	56— 64 h	64— 76 h	76— 88 h	88— 100 h	100— 128 h	0— 128 h
Mean mEq/l	1 70	1.65	1.68	1.84	1 75	1.72	1.67	1 63	1 73	1.73	1 77	1 73	1 77	1 71
SD	0.25	0.22	0.26	0.30	0.24	0.26	0.23	0.20	0.22	0.22	0.20	0.23	0.23	0.23
Number of observations	20	10	22	25	27	24	23	30	26	30	25	28	13	322

TABLE 12

MAGNESIUM, CALCIUM AND PHOSPHORUS LEVELS DURING THE FIRST FIVE DAYS IN 30 INFANTS WITH A GESTATIONAL AGE 28—36 WEEKS

	Age h 0—2	2—8	8—16	16— 24	24— 32	32— 40	40— 48	48— 56	56— 64	64— 76	76— 88	88— 100	100— 128
Magnesium													
Mean mEq/l	1.91	1.80	1.88	1.88	1 78	1.91	1.84	1.85	1.86	1.80	1.93	1.90	1.85
SD	0.31	0.34	0.34	0.39	0.27	0.29	0.29	0.28	0.31	0.28	0.39	0.36	0.33
Number of observations	14	12	22	24	23	21	21	23	21	22	19	17	21
Calcium													
Mean mEq/l	4.5	4.2	3.9	3.7	3.5	3.5	3.4	3.6	3.5	3.6	3.8	3.9	4.0
SD	0.6	0.7	0.7	0.7	0 7	0.7	0.6	0.8	0.7	0.6	0.6	0.5	0.5
Number of observations	14	14	25	26	25	24	27	24	25	27	25	21	23
Phosphorus													
Mean mg/100 ml	7 4	6 5	6.9	7 4	7 1	7 9	7.9	7.0	6.9	6.7	6.7	6.3	6.1
SD	2.2	2.9	2.2	2 9	1 7	1.8	1.6	1 7	2.0	2.0	2.2	1.6	2.0
Number of observations	15	12	22	22	25	22	22	23	21	23	20	18	20

TABLE 13.

MAGNESIUM, CALCIUM AND PHOSPHO US LEVELS DURING THE FIRST FIVE DAYS N 87 INFANTS WITH A GESTATIONAL AGE OF 37—44 WEEKS

	Age h 0—2	2—8	8—16	16—24	24—32	32—40	40—48	48—56	56—64	64—76	76—88	88—100	100—128
Magnesium													
Mean mEq/l	1 70	1 67	1 70	1 77	1 69	1 70	1 68	1 72	1 71	1 72	1 73	1 70	1 79
SD	0.27	0.25	0.32	0.29	0.26	0.26	0.25	0.29	0.27	0.29	0.28	0.28	0.29
Number of observations	46	29	64	59	72	65	65	68	63	62	53	54	39
Calcium													
Mean mEq/l	4 7	4 6	4.3	4 1	4 1	4.1	4 0	4.1	4 0	4 0	4.1	4.2	4 3
SD	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.6	0.5	0.5	0.6	0.6	0.7
Number of observations	60	44	76	75	79	73	73	78	72	74	62	63	45
Phosphorus													
Mean mg/100 ml	6.8	6.4	7 0	7 0	6.9	7.3	7 6	7 7	7.8	7 6	7.3	7.3	7.2
SD	2.3	2.0	0	2.3	2.1	1.8	2.0	2.0	2.2	2.2	1 8	1.9	2.0
Number of observations	53	34	59	65	68	65	66	68	64	61	56	55	36

TABLE 14

MAGNESIUM, CALCIUM PHOSPHO US LEVELS DURING THE FIRST FIVE DAYS IN 44 LOW IRTH WEIGHT INFANTS (< 2 500 o)

	Age h 0—2	2—8	8—16	16—24	24—32	32—40	40—48	48—56	56—64	64—76	76—88	88—100	100—128
Magnesium													
Mean mEq/l	1.80	1 69	1 78	1 79	1 70	1 83	1 75	1.82	1 80	1.85	1.93	1.86	1.88
SD	0.24	0.33	0.32	0.34	0.27	0.29	0.30	0.30	0.31	0.28	0.34	0.29	0.30
Number of observations	18	17	30	34	33	33	31	33	30	29	28	23	26
Calcium													
Mean mEq/l	4 4	4 3	4 0	3.9	3.9	3.9	3.7	4.0	3.7	4.0	4.0	4.0	4 1
SD	0.6	0.7	0.8	0.7	0.8	0.7	0.6	0.7	0.8	0.6	0.6	0.7	0.7
Number of observations	21	24	35	41	37	37	36	37	34	37	36	30	30
Phosphorus													
Mean mg/100 ml	7 6	6.1	6.7	7 0	6.9	7.3	7.6	6.8	7 0	6.5	6.4	6.3	5.8
SD	2.6	2 4	2.1	3.0	2.4	1 7	2.2	1.8	2.0	2.0	1.9	1.9	1 7
Number of observations	..0	19	34	35	36	34	36	36	33	31	31	26	26

TABLE 15.

MAGNESIUM, CALCIUM AND PHOSPHORUS LEVELS DURING THE FIRST FIVE DAYS IN 73 FULL BIRTH WEIGHT INFANTS (≥ 2 500 g)

	Age h 0—2	2—8	8—16	16—24	24—32	32—40	40—48	48—56	56—64	64—76	76—88	88—100	100—128
Magnesium													
Mean mEq/l	1.73	1.72	1.73	1.81	1.71	1.70	1.70	1.71	1.72	1.69	1.68	1.70	1.76
SD	0.31	0.25	0.34	0.31	0.27	0.26	[illegible]	0.28	0.27	0.28	0.28	0.31	0.29
Number of observations	42	4	56	49	62	53	55	58	55	53	44	48	34
Calcium													
Mean mEq/l	4.8	4.6	4.3	4.1	4.1	4.0	3.9	4.0	4.0	3.9	4.1	4.2	4.2
SD	0.5	0.5	0.6	0.6	0.5	0.5	0.6	0.6	0.5	0.6	0.6	0.5	0.6
Number of observations	53	34	65	60	68	60	64	65	63	64	51	54	39
Phosphorus													
Mean mg/100 ml	6.7	6.7	7.2	7.1	7.0	7.5	7.7	7.9	7.9	7.8	7.6	7.5	7.7
SD	2.1	2.1	2.0	2.2	1.8	1.8	1.6	1.9	2.3	2.1	1.8	1.8	1.9
Number of observations	48	27	47	52	56	53	52	53	52	53	43	47	30

TABLE 16.

MAGNESIUM, CALCIUM AND PHOSPHORUS LEVELS DURING THE FIRST FIVE DAYS IN 9 INFANTS OF DIABETIC MOTHERS.

	Age h 0—2	2—8	8—16	16—24	24—32	32—40	40—48	48—56	56—64	64—76	76—88	88—100	100—128
Magnesium													
Mean mEq/l	2.13	1.88	2.12	1.98	1.89	1.83	1.82	1.77	1.82	1.59	1.72	1.87	1.69
SD	0.17	0.04	0.21	0.28	0.25	0.19	0.21	0.32	0.29	0.20	0.37	0.50	0.38
Number of observations	6	4	5	5	7	6	6	6	6	7	6	6	9
Calcium													
Mean mEq/l	4.6	4.3	4.0	3.7	3.7	3.4	3.1	3.2	3.4	3.3	3.3	3.7	4.0
SD	0.3	0.5	0.3	0.6	0.5	0.5	0.5	0.6	0.6	0.5	0.6	0.5	0.6
Number of observations	6	4	5	5	7	6	6	6	6	7	6	6	9
Phosphorus													
Mean mg/100 ml	8.3	6.7	7.2	8.1	7.5	8.3	8.6	8.0	7.7	7.8	7.9	8.3	7.9
SD	2.5	1.2	1.3	1.6	1.9	[illegible]	1.3	0.8	1.0	1.6	1.4	1.2	1.7
Number of observations	6	4	5	5	7	7	6	6	6	7	6	6	9

TABLE 17

MAGNESIUM, CALCIUM AND PHOSPHORUS LEVELS DURING THE FIRST FIVE DAYS IN 10 LOW BIRTH WEIGHT INFANTS OF TOXEMIC MOTHERS.

	Age h 0—2	—8	8—16	16—24	24—32	32—40	40—48	48—56	56—64	64—76	76—88	88—100	100—128
Magnesium													
Mean mEq/l	1.77	1.58	1.57	1.64	1.43	1.73	1.50	1.68	1.60	1.69	1.84	1.68	1.76
SD	0.20	0.21	0.22	0.23	0.18	0.26	0.26	0.41	0.23	0.25	0.40	0.34	0.35
Number of observations	7	5	6	9	9	8	7	8	8	8	6	6	7
Calcium													
Mean mEq/l	4.7	4.7	4.7	4.4	4.2	4.1	4.1	4.1	3.9	4.2	4.2	4.4	4.5
SD	0.5	0.4	0.3	0.6	0.5	0.6	0.5	0.7	0.6	0.5	0.5	0.4	0.4
Number of observations	7	5	6	9	9	8	7	8	8	8	6	6	7
Phosphorus													
Mean mg/100 ml	6.7	4.9	5.7	6.0	6.3	7.2	6.9	6.3	6.1	5.6	5.7	6.0	5.9
SD	3.1	0.7	2.3	2.9	2.0	2.0	1.9	1.3	1.5	1.4	1.3	1.5	1.0
Number of observations	7	5	6	9	9	8	7	8	8	8	6	6	7

List of Supplements to Acta Paediatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

161. Peltonen, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr 20.— 1966
166. *Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis.* Analysis of 544 Cases. Sw. kr 25.— 1966
167 Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children, Longitudinal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr 30. — 1966
170. Bellman, Margot, Studies on Encopresis. Sw kr 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr 20.— 1966
172. *Festschrift in Memory of Constantin Choremis.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw kr. 15.— 1967
174. Petersson, Per Owe, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Ilmanen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress.* Bergen. 1967 Sw. kr. 35.— 1967
178. Sjögren, Irène, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968

Koch, Göran, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968

Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968

183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.— 1968
185. Andersen, Elso, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr 40.— 1968
186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968
187. Karlberg, Petter, *et al.*, The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I-VI. Sw. kr 30.— 1968
188. Meeuwisse, Gunnar W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr 20.— 1969
190. *Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing.* Sw. kr. 20.— 1969
191. Koivikko, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality 1969
194. Kamento, Antti, Studies on the Serum Binding of Vitamin B_{12} in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969
197 Sunila, Ritva, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Sanjur, Diva M., Cravioto, Joaquín, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201 Sutherland, Lynette E., Hartroft, Phyllis, Balis, John U., Bailey, John D. and Lynch, Matthew J., Bartter Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr 30.— 1970
202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr 30.— 1970
203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr 35.— 1970
204. Berg, Kristian, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress.* Turku, August 3–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207 Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 35.— 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. Sw. kr 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr 25.— 1971
212. Hakulinen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr 25.— 1971
214. Samuelson, Gösta, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw kr 25.— 1971
215. Berggren, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr. 25.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium,* Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. Sw kr. 35.— 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 35.— 1971
219 *Jaffé, Doris, Hartwell, Stanley, Manning, Mary and Eleta, Graciela,* Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. Sw kr. 25.— 1971
220. Hallman, Niilo, Bäckström, Leena, Kantero, Riitta-Liisa and Tiisala, Ritva, Studies on Growth of Finnish Children from Birth to Ten Years. Sw. kr. 30 — 1971
221. Bohman, Michael, A Comparative Study of Adopted Children, Foster Children and Children in Their Biological Environment Born after Undesired Pregnancies. Sw. kr. 35.— 1971
222. Jukarainen, Erkki, Plasma Magnesium Levels during the First Five Days of Life. Sw. kr. 30.— 1971

Price Swed. kr 30 —

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

[illegible]

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 223 197

FOOD CONSUMPTION AND GROWTH OF NORMAL INFANTS FED MILK BASED FORMULAS

BY SAMUEL J FOMON LORA N THOMAS,
L. J FILER Jr., EKHARD E. ZIEGLER
AND MICHAEL T LEONARD



ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

This work was supported by United States Public Health
Service Research Grant No. HD 00383.

Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
UPPSALA 1971

The feasibility of obtaining reliable records of daily food intake of normal infants living in their own homes has come about through a combination of circumstances. We are situated in a University community where well educated parents are willing to make their infants available for study. A tradition of mutual trust has been established between the investigators and the young people of the community. Within the past few years, ready-to-feed infant formulas have become available and advances in computer technology have made it relatively easy to record a large amount of information on a daily basis.

The formulas chosen for this study were all prepared from fat free cow milk and vegetable oils (in one instance, vegetable oils and butterfat) with the addition of various carbohydrates. They provided 67 kcal/100 ml with 7 to 13% of calories from protein, 41 to 48% of calories from carbohydrate and 38 to 52% of calories from fat. They were either commercially available or similar in many respects to commercially available formulas fed to hundreds of thousands of infants in the United States each year. Thus, it was believed that observations of normal infants fed these formulas ad libitum could provide normative data that would be useful for at least three purposes: evaluation of other formulas providing 67 kcal/100 ml, study of factors influencing food consumption by normal infants, and assessment of performance of individual infants suspected of abnormality.

SUBJECTS

Normal, fullterm Caucasian infants with birth weights of 2 500 g or more whose mothers had decided upon formula feeding rather than breast feeding were considered eligible for enrollment in the study. Only those infants were accepted whose parents indicated willingness to comply with the prescribed protocol. The observations presented in this report concern infants studied between January 1966 and April 1970 who were fed formulas providing 67 kcal/100 ml and protein from fat free cow milk. Not included here are observations of infants fed formulas of different caloric concentrations or formulas with protein from other sources. Infants who served as subjects for metabolic balance studies were considered ineligible for inclusion because they did not live continuously at home with their parents as did the other infants.

Because most of the formulas were not commercially available, the major factor in determining sequence of feeding was availability of the formula. Once a formula had been delivered to us by a manufacturer we studied it as soon as possible. After enrollment of the first infant in a feeding group every formula-fed infant of that sex subsequently enrolled was assigned to the same feeding group until the agreed upon number of subjects had been enrolled.

Nearly all of the subjects were children of students or younger staff members of the University of Iowa and several were siblings of children who had served as subjects of other studies reported from the Infant Metabolic Unit in recent years.

Table I indicates for each feeding group the number of subjects who completed 111 days of study and the mean and range of birth weights for these subjects. Birth weights for individual subjects of both the complete and

---

There were two exceptions to these stipulations for inclusion of infants in the study: one female infant (Subject 1379) had birth weight of 2 470 g and another female infant (Subject 983) served as subject for metabolic balance studies. Computer analyses of the data had been completed before we discovered that these infants had been included. Data concerning Subjects 1379 and 983 may be identified in the Appendices.

This work was supported by United States Public Health
Service Research Grant No. HD 00383.

Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
UPPSALA 1971

Table 2. *Composition of formulas*

Components	3215A	29B	5024A	3221A	3215E	5018C	Similac	Formil	Modilac
Fat (% of total fat)									
Corn oil	80	50	50	40	60		50	25	100
Coconut oil	20	50	50	20			50	.5	
Soy oil				40		100			
MCT					40				
Butterfat								50	
Added carbohydrate									
Lactose									
Corn syrup solids									
Major constituents (g/100 ml)[a]									
Protein	1.3	1.1	1.6	1.5	1.7	1.8	1.7	1.8	2.1
Fat	3.7	3.6	3.4	3.8	3.7	3.4	3.4	3.5	.7
Carbohydrate	6.9	7.8	7.0	7.0	7.0	7.4	6.6	7.0	7.8
Ash	0.34	0.25	0.40	0.34	0.34	0.40	0.40	0.40	0.40
Content of minerals (per liter)[a]									
Calcium, mg	552	426	667	584	520	700	658	663	862
Phosphorus, mg	459	312	542	518	483	507	524	543	662
Sodium, meq	16	10	11	—	—	11	11	11	17
Potassium, meq	16	13	28	—	—	[illegible]	28	15	27
Chloride, meq	13	11	15	—	—	15	15	13	19
Magnesium, mg	62	56	75	58	49	73	61	65	100
Iron (added), mg	—	8.2	—	—	—	—	[illegible]	9.2	10.0
Content of vitamins (per quart)									
Vitamin A, I.U	1 500	1 800	2 500	1 600	1 500	2 500	2 500	2 500	1 500
Thiamin, μg	400	900	670	400	400	670	670	500	500
Riboflavin, μg	1 000	1 600	1 000	600	1 000	1 000	1 000	900	1 000
Niacin, μg	4 000	2 900	4 200	7 000	4 000	4 200	4 200	6 000	6 000
Pyridoxine, μg	300	230	—	300	300	—	—	250	700
Pantothenate, μg	2 000	1 740	—	2 000	2 000	—	—	—	—
Ascorbic, mg	50	92	50	50	50	50	50	50	45
Vitamin D, I.U	400	400	400	400	400	400	400	400	400
Vitamin E, mg	5	3.4	5	8	5	5	5	—	5

[a] Italicized values indicate determinations from the laboratory of the investigators; other values are those reported to us by the manufacturers

to the prescribed protocol with respect to feeding of strained foods. Data on consumption of foods other than those already mentioned are summarized in Appendix V

PROCEDURES AND METHODS

The infants were weighed and measured between 6 and 9 days of age, within 2 days of each of the following ages: 14, 28, 42 and 56 days, and within 4 days of ages 84 and 112 days.

Weight was determined to the nearest 5 g with

Table 3. *Composition of strained foods*

Food	Proximate analysis (constituents per 100 g)[a]					
	kcal	Water (g)	Protein (g)	Fat (g)	Carbohydrate (g)	Density (g/ml)
Oatmeal with bananas and applesauce	77	80.6	1.5	0.9	15.6	1.070
Pears	68	81.4	0.3	0.1	16.4	1.081
Applesauce	87	77.7	0.2	0.2	21.2	1.088
Bananas	85	78.4	0.5	0.1	20.4	1.087

[a] Manufacturer's published analysis (Gerber Products Company 1965).

infant scales. Length was measured as described by Fomon (2). Two examiners measured each subject, one holding the head against the headboard while the other stretched the lower extremities, pressed the footboard firmly against the soles of the feet and noted body length. The two examiners then exchanged positions, repeated the procedure, and the average of the two measurements was recorded. When results of the two examiners differed by more than 0.4 cm, the measurements were repeated and the two values agreeing more closely were utilized.

INTERVALS OF STUDY

In describing size of the infants (e g., Appendices I and II) recorded measurements were corrected" by parabolic interpolation or extra polation utilizing three adjacent values to reflect values applicable to ages 8, 14 28, 42, 56, 84 and 112 days. For convenience these age designations have been employed throughout.

The day on which measurements of length and weight were made was employed as the *first day of the interval for recording food* intake. Thus, volume of intake and calorie intake were recorded for ages 8 through 13 days (8–13) 14 through 27 days (14–27) etc Gains in length and weight, on the other hand, are expressed as 8 to 14 (8–14) 14 to 28 (14–28) etc. When food intake data are included in a table that also provides data on gains in weight and/or length, the headings are listed as 8–13 14–27 etc.

RESULTS AND COMMENTS

One hundred and fifty-four infants, 69 males and 85 females were enrolled. The greater enrollment of females in this study of milk based formulas is explained by the enrollment of more males than females in concurrent studies of other formulas.

Data concerning growth of each infant are presented in Appendices I and II and data on food intake by each infant are presented in Appendices III–V Of the 154 infants enrolled, complete data were obtained for 142 (91%) through the planned 111-day period of observation. Analysis of the data is based on observations of these 142 infants.

Among the 12 infants for whom complete data were not available, only one (Subject 982) completed 112 days of study Complete food intake data for this infant could not be obtained during the age interval 84–111 days. The families of 4 Subjects (133 134 452 and 1325) moved from town Subject 453 was withdrawn from the study at the time of admission to the hospital for surgical correction of pyloric stenosis. Subject 1202 had casts applied for correction of bilateral equinovarus and was eliminated from the study because accurate measurements of weight and length could not be made, The parents of Subject 468 were reluctant to permit monthly venipuncture and therefore withdrew her from the study Two Subjects (986 and 1425) were withdrawn from the study at the request of the parents because of fussiness and/or regurgitation of formula. Subject 132 failed to appear for visits after age 14 days, and Subject 1384 missed the scheduled 14-day and 56-day appointments and was consequently eliminated from the study

Of the 142 infants who completed 111 days of observation, the feeding plan was modified in five instances for brief periods of time because of constipation (Subject 954) or diarrhea (Subjects 1362, 454 455 and 1422) Subject 954 received small amounts of Karo syrup during the age interval 28–41 days. Subject 1362 received Lytren[a] for several days during the age interval 42–55 days. Skim milk was fed for several days to three infants: Subject 454 during the age interval 84–111 days, Subject 455 during the age intervals 56–83 and 84–111 days, and Subject 1422 during the age interval 42–55 days. Average daily amounts of these foods consumed in the specified intervals are indicated in Appendix III.

Analysis of the data based on observations of the 142 infants who completed the planned 111 days of study will be presented in two parts: first, comparison of the various feeding groups second, analysis of the combined data

---
Continental Scales Company Chicago, Illinois.
Mead Johnson Company Evansville, Indiana.

for each sex from all feeding groups. The combined data on body size and on gain in weight and gain in length will be analyzed in relation to data on breastfed infants published previously (4)

Comparison of Feeding Groups

Between birth and the time of discharge from the Newborn Nursery nearly all infants received Similac or Enfamil[1] and in a number of instances this formula was continued until 7 to 9 days of age. No conclusion is therefore possible concerning the relation between allocation of formula and gain in weight during the first 8 days of life.

When infants are fed ad libitum by their parents, rather wide differences are noted in food consumption (volume of intake and intake of calories) whether expressed on an absolute basis (ml/day or kcal/day) or per unit of body weight. This is true even with respect to normal infants of the same sex fed the same diet. Therefore, we anticipated that statistically significant differences between feeding groups might be encountered with respect to mean volume of intake and/or mean intake of calories. Because of the demonstrated relation of gain in weight to intake of calories in our earlier studies (5 6), we anticipated that corresponding statistically significant differences in mean gains in weight might also be noted between feeding groups.

Table 4 presents data on volume of intake (ml/day and ml/kg/day) caloric intake (kcal/day and kcal/kg/day) and gain in weight (g/day and g/100 kcal) for each feeding group and for all males and all females during the following age intervals: 8–13 14–27 28–41 42–55, 56–83 84–111 and 8–111 days. It is evident that comparison of the various feeding groups might be made for any of these age intervals or for still other intervals (e.g., 8–27 8–42 days, etc.). However the comparisons presented here are restricted to the total interval, 8–111 days. Data in the appendices are available for comparisons of data pertaining to other age intervals.

Statistical analysis of differences in mean values between the various feeding groups have in all instances been performed by an analysis of variance which utilizes comparisons of mean values as described by Tukey (8 *a*).

Volume of intake and intake of calories

During the age interval 8–111 days, mean volumes of intake ranged from 753 ml/day for males fed Formula 3215E to 868 ml/day for males fed Formula 5024A (Table 4) and from 705 ml/day for females fed Formula 5018C to 804 ml/day for females fed Similac. On a sex specific basis, these differences are not statistically significant.[2] When volumes of intake were expressed per unit of body weight, mean intakes ranged from 146 ml/kg/day for males fed Formula 3215E to 168 ml/kg/day for males fed 5024A and from 138 ml/kg/day for females fed Formil to 167 ml/kg/day for females fed Similac. For each sex these feeding-related differences were statistically significant ($p < 0.05$)

As was anticipated, the ratio of volume of intake to intake of calories for each feeding group was slightly greater than 67 kcal/100 ml. Because of this relatively fixed ratio of caloric intake to volume of intake, the data concerning these two parameters ran closely in parallel. On a sex-specific basis, differences between feeding groups in caloric intakes (kcal/day) were not statistically significant. When expressed in relation to body weight (kcal/kg/day) statistically significant differences ($p < 0.05$) were demonstrated between feeding groups: mean intake by males fed Formula 5024A (114 kcal/kg/day) was significantly greater ($p < 0.05$) than that by males fed Formula 3215E (99 kcal/kg/day) or by those fed Formula 3221A (103 kcal/kg/day) mean intake by female infants fed Similac (113 kcal/kg/day) was significantly ($p < 0.05$) greater

---

[1] Mead Johnson Company E ansville, Indiana.

[2] Throughout this presentation, values of *p* greater than 0.05 are referred to as not statistically significant

infant scales. Length was measured as described by Fomon (2 a). Two examiners measured each subject, one holding the head against the headboard while the other stretched the lower extremities, pressed the footboard firmly against the soles of the feet and noted body length. The two examiners then exchanged positions, repeated the procedure, and the a erage of the two measurements was recorded. When results of the two examiners differed by more than 0.4 cm, the measurements were repeated and the two alues agreeing more closely were utilized.

INTERVALS OF STUDY

In describing size of the infants (e.g., Appendices I and II) recorded measurements were corrected" by parabolic interpolation or extrapolation utilizing three adjacent values to reflect values applicable to ages 8, 14 28, 42, 56 84 and 112 days. For convenience these a e designations have been employed through- t

The day on which measurements of length a ight were made was employed as the 'a of the interval for recording food k Thus, volume of intake and calorie i ta e we e recorded for ages 8 through 13 da (8–13) 14 through 27 days (14–27) etc. Gain in length and weight, on the other hand, are expressed as 8 to 14 (8–14), 14 to 28 (14–28) etc When food intake data are included in a table that also provides data on gains in weight and or length, the headings are listed as 8–13, 14–27 etc.

RESULTS AND COMMENTS

One hundred and fifty four infants, 69 males and 85 females, were enrolled. The greater enrollment of females in this study of milk based formulas is explained by the enrollment of more males than females in concurrent studies of other formulas.

Data concerning growth of each infant are presented in Appendices I and II and data on food intake by each infant are presented in Appendices III–V Of the 154 infants enrolled, complete data were obtained for 142 (91) through the planned 111-day period of observation. Analysis of the data is based on observations of these 142 infants.

Among the 12 infants for whom complete data were not available, only one (Subject 982) completed 112 days of study Complete food intake data for this infant could not be obtained during the age interval 84–111 days. The families of 4 Subjects (133 134 452 and 1325) moved from town. Subject 453 was withdrawn from the study at the time of admission to the hospital for surgical correction of pyloric stenosis. Subject 1202 had casts applied for correction of bilateral equinovarus and was eliminated from the study because ac curate measurements of weight and length could not be made, The parents of Subject 468 were reluctant to permit monthly venipuncture and therefore withdrew her from the study Two Subjects (986 and 1425) were withdrawn from the study at the request of the parents because of fussiness and/or regurgitation of formula. Subject 132 failed to appear for visits after age 14 days, and Subject 1384 missed the scheduled 14-day and 56-day appointments and was consequently eliminated from the study

Of the 142 infants who completed 111 days of observation, the feeding plan was modified in five instances for brief periods of time be cause of constipation (Subject 954) or diarrhea (Subjects 1362, 454 455 and 1422). Subject 954 received small amounts of Karo syrup during the age interval 28–41 days. Subject 1362 re ceived Lytren[2] for several days during the age interval 42–55 days. Skim milk was fed for several days to three infants: Subject 454 dur ing the age interval 84–111 days, Subject 455 during the age intervals 56–83 and 84–111 days, and Subject 1422 during the age interval 42–55 days. Average daily amounts of these foods consumed in the specified intervals are indicated in Appendix III.

Analysis of the data based on observations of the 142 infants who completed the planned 111 days of study will be presented in two parts. first, comparison of the various feeding groups second, analysis of the combined data

---
Continental Scales Company Chicago, Illinois
Mead Johnson Company E ans ille, Indiana

Table 4 (*continued*)

	Age interval (days)						
Formula	8–13	14–27	28–41	42–55	56–83	84–111	8–111
Males	*Calorie intake (kcal/day)*						
3215A	468 (35)	516 (25)	561 (35)	588 (36)	608 (36)	628 (27)	583 (27.1)
29B	342 (17)	45[illegible] (14)	509 (22)	546 (26)	570 (21)	619 (25)	543 (17.7)
5024A	377 (26)	492 (42)	577 (39)	613 (25)	619 (25)	646 (21)	589 (24.9)
3221A	399 (20)	484 (21)	535 (20)	543 (24)	561 (23)	607 (17)	548 (16.3)
3215E	384 (21)	440 (17)	473 (20)	524 (13)	529 (17)	565 (19)	510 (14.5)
Total	394 (11)	476 (12)	530 (13)	562 (11)	576 (11)	611 (10)	553 (9.6)
Females	*Calorie intake (kcal/day)*						
3215A	398 (22)	415 (18)	471 (17)	521 (21)	517 (14)	546 (19)	499 (11.2)
29B	332 (15)	428 (15)	442 (25)	466 (20)	503 (19)	555 (21)	484 (13.4)
5018C	339 (22)	410 (16)	476 (28)	477 (18)	507 (18)	511 (12)	477 (13.6)
Similac	394 (15)	470 (17)	547 (22)	536 (25)	558 (17)	604 (22)	544 (15.8)
Formil	402 (23)	425 (16)	456 (10)	480 (16)	497 (18)	526 (19)	482 (12.7)
Modilac	397 (25)	433 (21)	451 (18)	431 (16)	494 (15)	571 (18)	487 (13.9)
Total	382 (9)	431 (7)	476 (9)	487 (9)	513 (7)	552 (8)	497 (6.0)
Males	*Calorie intake (kcal/kg/day)*						
3215A	132 (10)	129 (6)	121 (8)	113 (7)	102 (5)	92 (2)	109 (3.9)
29B	102 (4)	122 (4)	120 (5)	115 (5)	106 (4)	101 (4)	110 (3.8)
5024A	109 (7)	126 (9)	130 (8)	123 (4)	109 (3)	100 (2)	114 (3.2)
3221A	110 (4)	120 (4)	116 (4)	106 (4)	97 (3)	93 (3)	103 (2.3)
3215E	108 (6)	113 (4)	105 (4)	105 (2)	94 (2)	89 (2)	99 (1.8)
Total	111 (3)	121 (3)	118 (3)	112 (2)	101 (2)	95 (1)	106 (1.5)
Females	*Calorie intake (kcal/kg/day)*						
3215A	113 (7)	107 (5)	108 (4)	108 (4)	95 (2)	89 (3)	100 (1.9)
29B	91 (4)	108 (5)	101 (7)	98 (4)	95 (2)	95 (4)	98 (2.1)
5018C	101 (7)	111 (5)	114 (5)	105 (4)	99 (3)	88 (2)	101 (2.6)
Similac	118 (5)	127 (4)	130 (5)	115 (5)	107 (3)	101 (3)	113 (2.7)
Formil	109 (7)	104 (5)	100 (2)	95 (3)	88 (2)	84 (2)	93 (1.8)
Modilac	112 (7)	110 (5)	103 (4)	91 (3)	94 (2)	97 (3)	99 (2.4)
Total	109 (3)	111 ([illegible])	110 (2)	102 (2)	96 (1)	92 (1)	101 (1.1)

Table 4 (*continued*)

Formula	Age interval (days)						
	8–13	14–27	28–41	42–55	56–83	84–111	8–111
Males	*Gain in weight (g/day)*						
3215A	34 (2)	48 (2)	42 (4)	37 (3)	35 (3)	26 (2)	35 (2.1)
29B	26 (4)	37 (2)	37 (2)	37 (4)	27 (2)	[illegible]6 (1)	31 (1.6)
5044A	32 (5)	43 (4)	38 (3)	38 (4)	30 (2)	29 (2)	34 (2.1)
3221A	36 (5)	42 ([illegible])	41 (2)	33 (3)	30 (2)	23 (2)	32 (1.6)
3215E	25 (3)	40 ([illegible])	41 (2)	33 (3)	28 (2)	[illegible]5 (2)	31 (1.3)
Total	31 (2)	42 (1)	40 (1)	35 (1)	30 (1)	[illegible]6 (1)	33 (0.7)
Females	*Gain in weight (g/day)*						
3215A	32 (2)	36 (2)	33 (3)	31 (2)	28 (2)	[illegible]1 (2)	[illegible]8 (1.6)
29B	[illegible]8 (4)	34 (2)	27 (4)	28 (2)	[illegible]3 (2)	20 (2)	25 (1.3)
5018C	30 (4)	34 (2)	30 (2)	29 (2)	26 (2)	22 (3)	27 (1.7)
Similac	33 (3)	38 (3)	34 (2)	30 (2)	[illegible] (2)	27 (3)	30 (1.3)
Formul	30 (4)	38 (3)	31 (2)	33 (3)	25 (2)	[illegible]2 (1)	28 (1.0)
Modulac	35 (3)	35 (2)	29 (2)	25 (2)	[illegible]5 (2)	21 (1)	26 (1.3)
Total	31 (1)	36 (1)	31 (1)	29 (1)	26 (1)	22 (1)	28 (0.6)
Males	*Gain in weight per unit of calorie intake (g/100 kcal)*						
3215A	7.5 (0.6)	9.4 (0.5)	7.7 (0.7)	6.2 (0.3)	5.8 (0.3)	4.0 (0.2)	6.1 (0.2)
29B	8.[illegible] (1.8)	8.[illegible] (0.5)	7.4 (0.5)	6.7 (0.5)	4.8 (0.3)	4.3 (0.3)	5.7 (0.2)
5044A	8.2 (0.8)	8.7 (0.4)	6.5 (0.3)	6.[illegible] (0.6)	4.9 (0.3)	4.4 (0.2)	5.7 (0.2)
3221A	9.1 (1.0)	8.9 (0.5)	7.7 (0.4)	6.1 (0.4)	5.3 (0.3)	3.9 (0.4)	5.9 (0.3)
3215E	7.0 (0.9)	9.1 (0.5)	8.8 (0.3)	6.2 (0.5)	5.3 (0.2)	4.4 (0.3)	6.1 (0.2)
Total	8.0 (0.5)	8.9 (0.2)	7.6 (0.2)	6.3 (0.2)	5.2 (0.1)	4.[illegible] (0.1)	5.9 (0.1)
Females	*Gain in weight per unit of calorie intake (g/100 kcal)*						
3215A	8.4 (0.8)	8.6 (0.5)	7.0 (0.6)	6.0 (0.4)	5.3 (0.3)	3.8 (0.3)	5.6 (0.2)
29B	8.5 (0.9)	7.9 (0.3)	5.9 (0.6)	5.8 (0.4)	4.5 (0.3)	3.6 (0.4)	5.1 (0.3)
5018C	9.1 (1.4)	8.3 (0.3)	6.3 (0.5)	6.0 (0.4)	5.1 (0.4)	4.3 (0.5)	5.7 (0.3)
Similac	8.4 (0.8)	8.0 (0.5)	6.2 (0.4)	5.6 (0.3)	4.8 (0.2)	4.4 (0.5)	5.5 (0.2)
Formul	8.1 (1.[illegible])	8.9 (0.7)	6.7 (0.3)	6.8 (0.4)	5.0 (0.3)	4.[illegible] (0.[illegible])	5.8 (0.2)
Modulac	9.[illegible] (1.[illegible])	8.[illegible] (0.6)	6.5 (0.4)	5.8 (0.3)	4.9 (0.3)	3.7 (0.2)	5.4 (0.2)
Total	8.6 (0.4)	8.4 (0.[illegible])	6.5 (0.[illegible])	6.0 (0.[illegible])	5.0 (0.1)	4.0 (0.[illegible])	5.6 (0.1)

than mean intakes by females fed Formil (93 kcal/kg/day) or Formula 29B (98 kcal/kg/day)

Gains in weight and length

During the interval 8–112 days of age, mean gains in weight by male infants ranged from 31 g/day by those fed Formulas 29B and 3215E to 35 g/day by those fed Formula 3215A (Table 4). Mean gains in weight by female infants during this age interval ranged from 25 g/day by those fed Formula 29B to 30 g/day by those fed Similac. Mean gains in weight per unit of calorie intake by males ranged from 5 7 g gain per 100 kcal (infants fed Formulas 29B and 5024A) to 6.0 g gain per 100 kcal (infants fed Formulas 3215A and 3215E) Similar gains by females ranged from 5 1 by those fed Formula 29B to 5 8 by those fed Formil. On a sex specific basis, none of these feeding-related differences was statistically significant.

Mean gains in length by male infants during the interval 8–111 days of age ranged from 1 08 mm/day by those fed Formula 3215E to 1 17 mm/day by those fed Formula 3215A. Mean gains in length by female infants ranged from 1 00 mm/day by those fed Formula 29B to 1.06 mm/day by those fed Modilac and Formula 5018C. Mean gains in length per unit of calorie intake by males ranged from 0.20 mm gain per 100 kcal consumed by infants fed Formulas 5024A and 29B to 0.21 mm gain per 100 kcal consumed by those fed Formulas 3215A, 3215E and 3221A. Corresponding mean gains by females ranged from 0.20 mm gain per 100 kcal consumed by those fed Similac to 0.23 mm gain per 100 kcal consumed by those fed Modilac and Formula 5018C. On a sex specific basis, these differences were not statistically significant

Combined Data

This section of the report summarizes the data for each sex, combining information from all of the studies with milk-based formulas. In addition, data on weight and length and on gain in weight and gain in length are compared with those from our previous study of breast fed infants. For purposes of this comparison, data are restricted to observations of breastfed and formula fed infants who completed the planned 112 days of observation Statistical analysis of differences in mean values between formula-fed males and formula-fed females or between breastfed and formula-fed infants of the same sex have been performed by a two-sample t'' test (8 *b*).

Table 5. *Summary of food intake data: percentile values*

	Age interval (days)					
Percentile	8–13	14–27	28–41	42–55	56–83	84–111
Males						
	Volume of intake (ml/day)					
10th	436	541	607	680	671	742
50th	573	696	774	790	846	890
90th	741	865	988	1 028	1 033	1 030
	Volume of intake (ml/kg/day)					
10th	122	142	134	137	123	118
50th	166	181	172	161	148	137
90th	208	214	209	198	178	155
	Calorie intake (kcal/day)					
10th	292	362	408	456	455	503
50th	383	464	520	531	568	617
90th	496	580	665	701	700	706
	Calorie intake (kcal/kg/day)					
10th	82	95	91	91	83	81
50th	111	121	116	108	100	96
90th	142	143	140	133	119	106
Females						
	Volume of intake (ml/day)					
10th	417	511	565	573	648	674
50th	558	657	695	721	741	791
90th	745	757	854	855	909	975
	Volume of intake (ml/kg/day)					
10th	116	125	128	119	125	116
50th	160	169	159	153	137	133
90th	208	197	195	182	164	756
	Calorie intake (kcal/day)					
10th	279	342	382	386	437	463
50th	374	440	470	489	500	545
90th	500	508	573	577	612	654
	Calorie intake (kcal/kg/day)					
10th	82	86	90	83	87	82
50th	113	117	111	108	97	94
90th	143	136	136	125	114	109

Table 6. *Summary of data on food intake and growth*

	Males			Females		
	Age interval (days)			Age interval (days)		
	8–55	56–111	8–111	8–55	56–111	8–111
Volume of intake (ml/day)	735 (124)[a]	870 (118)	815 (114)	660 (85)	785 (90)	734 (79)
Volume of intake (ml/kg day)	169 (25)	143 (15)	157 (17)	157 (22)	139 (14)	145 (15)
Calorie intake (kcal/day)	495 (84)	593 (81)	553 (77)	458 (60)	548 (62)	497 (53)
Calorie intake (kcal/kg day)	114 (17)	98 (10)	106 (12)	109 (15)	97 (9)	101 (10)
Gain in weight (g/day)	38.0 (7.7)	27.9 (6.6)	3[illegible].6 (6.4)	31.9 (6.1)	23.9 (5.6)	27.6 (5.1)
Gain in weight (g/100 kcal)	7.5 (1.1)	4.7 (0.8)	5.9 (0.7)	7.0 (1.0)	4.5 (0.9)	5.6 (0.8)
Gain in length (mm/day)	1.27 (0.15)	1.00 (0.15)	1.12 (0.11)	1.22 (0.16)	0.91 (0.13)	1.05 (0.10)
Gain in length (mm/100 kcal)	0.26 (0.04)	0.17 (0.03)	0.21 (0.03)	0.27 (0.04)	0.17 (0.03)	0.21 (0.03)

Values in parentheses are standard deviations.

Food consumption

Included in Table 4 are summary data on mean volume of intake (ml/day and ml/kg/day) and mean calorie intake (kcal/day and kcal/kg/day) for all males and females for the following age intervals: 8–13, 14–27, 28–41, 42–55, 56–83, 84–111 and 8–111 days. The 10th, 50th and 90th percentile values for intake by all males and all females during all but the last of these intervals are presented in Table 5. The mean and standard deviation for volume of intake (ml/day and ml/kg/day) and

Table 7. *Relation of volume of intake and calorie intake to body weight during six consecutive age intervals*

Age interval (days)	Regression[a] equation	Correlation coefficient	Residual variance S^2	Age interval (days)	Regression[a] equation	Correlation coefficient	Residual variance S^2
	Volume of intake (ml/day)				*Calorie intake (kcal/day)*		
Males				Males			
8–13	Y 128x 134	0.33	131	8–13	Y = 86x + 90	0.33	88
14–27	Y 161x 78	0.42	132	14–27	Y 108x + 52	0.42	89
28–41	Y 160x 65	0.43	141	28–41	Y 107x + 48	0.42	97
42–55	Y 13[illegible]x 167	0.44	1[illegible]4	42–55	Y = 89x + 114	0.44	84
56–83	Y 150 6	0.60	108	56–83	Y = 103x − 14	0.60	74
84–111	Y 108x 19	0.62	91	84–111	Y = 75x + 128	0.61	63
Females				Females			
8–13	Y 38 435	0.13	120	8–13	Y = [illegible]5x 291	0.13	80
14–27	Y 36x 503	0.14	96	14–27	Y [illegible]4x 337	0.14	65
28–41	Y 65 4[illegible]	0.[illegible]	114	28–41	Y = 4[illegible]x 292	0.21	77
42–55	Y 103 [illegible]27	0.36	108	42–55	Y 70x 151	0.37	73
56–83	Y 103 10	0.49	81	56–83	Y = 69x 147	0.48	55
84–111	Y 104 184	0.47	97	84–111	Y 66x + 158	0.44	67

[a] Y is volume of intake (ml/day) or caloric intake (kcal/day) and x is body weight (kg).

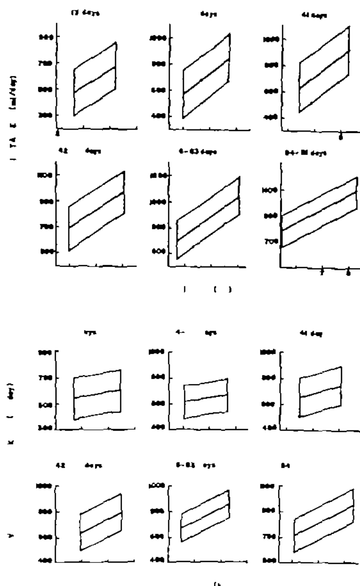


Fig. 1. Regressions of volume of intake on body weight of males (upper) and females (lower) during six successive age intervals. The stippled areas indicate the 90% confidence ranges.

for caloric intake (kcal/day and kcal/kg/day) are summarized in Table 6 for males and for females during the age intervals 8–55, 56–111 and 8–111 days.

Volume of intake and caloric intake. Food consumption (ml/day or kcal/day) increased with increasing age; per kilogram of body weight, intakes were greatest in the interval 14 through 27 days (Tables 4 and 5).

Food consumption (ml/day or kcal/day) was greater by males than by females (Tables 4–6). During the interval 8–111 days of age, mean volumes of intake by males and females were 815 and 734 ml/day, respectively (standard errors of the mean 14.1 and 9.0—Table 4); corresponding mean intakes of calories were 553 and 497 kcal/day (S.E. 9.0 and 6.0). These sex related differences are statistically significant ($p < 0.05$).

As has been noted (see Comparison of Feeding Groups) statistically significant differences were found in food consumption per *unit of* body weight (ml/kg/day and kcal/kg/day). For this reason, the sex related comparison of

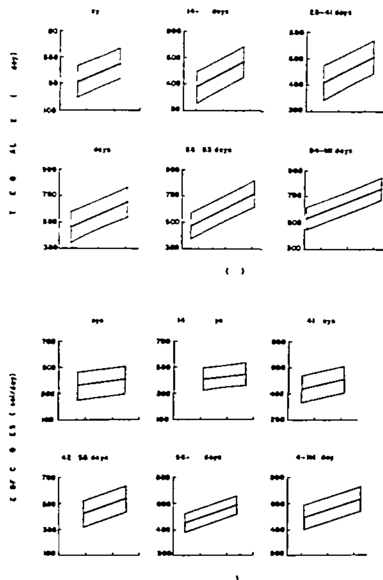


Fig 2 Regressions of calorie intake on body weight of males (upper) and fe males (lower) during six successive age intervals. The stippled areas indicate the 90% confidence ranges.

food consumption per unit of body weight has been restricted to data concerning those in fants fed Formulas 3215A and 29B As may be seen from Table 1 21 males and 22 females received these feedings During the interval 8–111 days of age mean volumes of intake were 161 and 146 ml kg day for males and females, respectively (S E 4 0 and 2.1) and mean calorie intakes by male and female infants were 109 and 99 kcal kg day re spectively (S.E. ?6 and 1 4) These sex-re lated differences are statistically significant ($p < 0.01$).

Regression equation (9) for volume of intake (ml/day) on body weight are presented in Table 7 for six successive age intervals. The extent to which volume of intake in-creased with increasing age and size may be seen from Fig. 1

As already mentioned, each formula pro-vided 67 kcal/100 mL During the age intervals 8–13 and 14–27 days, when formula served as sole source of calories, it is evident that calorie intake can be calculated from the data on volume of intake Although older infants were permitted to consume strained foods with caloric densities greater than 67 kcal/100 ml (Table 3) it may be noted (Table 4) that in

the age interval 84 through 111 days, volume of intake by males averaged 890 ml/day and corresponding intake of calories averaged 611 kcal/day Thus, caloric density of the total diet was 68.6 kcal/100 ml.

The relation between calorie intake (kcal/day), age and size may be seen from Table 7 and Fig. 2. Although it is not readily apparent from inspection of Fig. 2, one may calculate from the regression equations presented in Table 7 that at a specified body weight, calorie intake (kcal/day) decreased with increasing age· for example, mean calorie intakes of 5 kg male infants in the age intervals 28–41 42–55 and 56–83 days may be calculated to be 583, 559 and 501 kcal/day· mean calorie intakes of 6 kg male infants in the age intervals 42–55 56–83 and 84–111 days are 648, 604 and 578 kcal/day Presumably the greater calorie intakes by younger infants of a specified age reflect the greater calorie needs of these more rapidly growing individuals.

In each age interval, the equations presented in Table 7 indicate that the mean calorie intake for a specified weight by female infants is less than the corresponding mean intake by male infants. This difference is explained at least in part by the less rapid rate of gain by female than by male infants of a specified age and size

Size and gain

Size The 10th, 25th, 50th, 75th and 90th percentile values for weights and lengths of infants who completed 112 days of study are presented in Table 8 for breastfed infants (4) and those fed milk-based formulas. Values for weight at birth and for weight and length at ages 8, 14 28, 42, 56, 84 and 112 days are included. The 10th, 50th and 90th percentile values for lengths and weights of infants fed the milk-based formulas may be seen from Fig. 3 Also included in Fig. 3 is the 10th to 90th percentile range for breastfed infants studied previously (4)

Birth weights of male and female infants of the formula-fed series (Table 8 and Fig. 3)

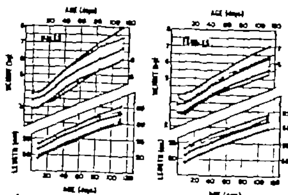


Fig 3. Weights and lengths of formula-fed and breastfed infants between birth and 112 days of age. The heavy lines indicate the 10th, 50th and 90th percentile values for formula-fed infants (see Table 8). The shaded areas include the 10th to the 90th percentile values for weight and length of breastfed infants studied previously (4).

were not remarkably different. The 50th percentile value was 60 g greater for males than for females. The 90th percentile value was actually greater for females than for males. At age 8 days (the first recorded measurement of length) the 50th percentile value for length was 0.6 cm greater for males than for females.

By 56 days of age, the difference in size between male and female infants of the [illegible] fed series had increased. The 50th [illegible] value was 302 g greater in weight [illegible] greater in length for males than for [illegible] By 112 days of age, the 50th percen[illegible] for weight and length of male [illegible] fants differed by 409 g and 1 [illegible]

The 10th, 50th and 90th [illegible] for weight at birth were [illegible] male infants of the breastfe[illegible] of the formula-fed series. [illegible] the 10th percentile values [illegible] infants of the two series [illegible] their 50th and 90th percentile [illegible] (215 g and 687 g, respe[illegible] formula-fed than for [illegible] series. The 10th, [illegible] values for length at [illegible] for male infants of [illegible] for those of the br[illegible] of age, the 50th [illegible] values [illegible]

Table 8. *Size of breastfed infants and those fed milk-based formulas, percentile values*

		Weight (kg)				Length (cm)			
		Males		Females		Males		Females	
Age (days)	Percentile	Fed milk based formulas (65)[a]	Breast fed (58)	Fed milk based formulas (77)	Breast-fed (46)	Fed milk based formulas (65)	Breast-fed (58)	Fed milk based formulas (77)	Breast-fed (46)
Birth	10	870	2 947	2 816	2 798				
	25	3 125	3 16	3 135	994				
	50	3 410	3 470	3 350	3 188				
	75	3 705	3 642	3 615	3 520				
	90	3 804	3 916	3 964	3 730				
8	10	2 878	2 881	2 903	2 746	48.9	49.5	48.8	48.5
	25	3 48	3 216	3 774	978	50.1	50.4	49.9	49.5
	50	3 502	3 459	3 401	3 260	51.7	51.2	51 1	50.7
	75	3 688	3 642	3 698	3 465	52.6	52.3	52.0	51 4
	90	3 906	3 839	4 031	3 555	53.4	52.8	53.2	52.2
14	10	3 13	3 089	3 1 4	2 990	49.8	50.6	49.4	49 7
	25	3 399	3 375	3 426	3 199	50.9	51.5	50.7	50.4
	50	3 665	3 681	3 575	3 500	52.6	52.4	52.0	51 6
	75	3 876	3 881	3 894	3 630	53.4	53.3	53.0	52.2
	90	4 089	4 065	4 177	3 698	54 1	54.2	54.1	53.4
28	10	3 636	3 406	3 605	3 511	51 6	52.0	51.5	51.6
	25	3 970	3 960	3 824	3 763	52.8	53.3	52.4	52.0
	50	4 235	4 271	4 134	3 935	54.6	54.2	53 8	53.3
	75	4 470	4 507	4 440	4 148	55.3	55.1	55 1	53.9
	90	4 761	4 69	4 593	4 230	55.9	55.7	56.0	55.0
42	10	4 250	3 962	4 028	3 930	53.0	53.8	53.0	53.2
	25	4 506	4 466	4 275	4 136	54.8	54.8	54 0	53.7
	50	4 828	4 808	4 579	4 360	56.2	56.0	55.2	54 7
	75	5 080	5 040	4 915	4 600	57.3	56.8	56.5	55.5
	90	5 437	5 312	5 060	4 692	57 7	57.5	57 6	56.6
56	10	4 685	4 387	4 441	4 43	54.3	55.2	54 6	54.6
	25	4 967	4 933	4 603	4 498	56.3	56.3	55.3	55 1
	50	5 255	5 250	4 953	4 758	57.6	57 6	56.8	56.3
	75	5 599	5 550	5 308	4 959	58.7	58.4	58.1	56.9
	90	5 918	5 791	5 500	5 161	59.3	59 4	59.2	57 7
84	10	5 292	5 320	5 000	4 707	57.8	58.3	57.0	57.2
	25	5 740	5 589	5 388	5 161	59.3	59.0	58.2	57 7
	50	5 973	5 955	5 675	5 424	60.8	59.9	59.5	58.6
	75	6 501	6 236	6 027	5 654	61.6	61.0	60.8	59 7
	90	7 015	6 773	6 357	5 800	62.6	61.9	61 7	60.2
112	10	5 949	5 933	5 568	5 212	60.1	61 1	59.6	59 7
	25	6 305	6 186	5 976	5 512	61 4	61.8	60.3	60 0
	50	6 697	6 442	6 288	5 987	63.0	62.6	61.9	60.9
	75	7 253	7 051	6 669	6 204	64.5	63.8	63.2	62.2
	90	7 993	7 306	7 018	6 428	65.4	64.2	64 0	63.1

[a] Values in parentheses are number of subjects.

were similar for the formula-fed and breastfed infants but the 90th percentile value for length was 1.2 cm greater for infants of the formula-fed series.

In the case of female infants the 10th percentile values for weight at birth were similar for infants of the formula fed and breastfed series but the 50th and 90th percentile values for weight at birth were greater (by 162 and 234 g, respectively) for infants of the formula fed series. By 112 days of age, the 10th, 50th and 90th percentile values for weight were

Table 9 *Daily change in weight (g/day) between selected ages*

Age (days)	Per centile	8 days	14 days	28 days	42 days	56 days	84 days	112 days
Males								
Birth	10	−12	3	20	25	25	24	24
	25	−7	10	25	29	29	29	26
	50	7	17	29	33	33	32	30
	75	19	23	34	38	39	36	34
	90	25	28	38	40	43	42	40
8	10		12	29	30	29	26	25
	25		21	33	34	32	31	28
	50		30	38	38	36	34	32
	75		37	45	45	43	38	35
	90		54	51	49	48	46	43
14	10			30	33	30	26	25
	25			36	36	33	30	27
	50			41	40	38	35	32
	75			50	46	43	38	35
	90			54	51	50	48	44
28	10				29	26	25	23
	25				33	31	28	27
	50				38	36	33	30
	75				45	42	38	35
	90				56	52	46	43
42	10					22	22	21
	25					26	24	24
	50					34	32	30
	75					41	36	34
	90					53	46	41
56	10						20	19
	25						23	23
	50						31	28
	75						34	32
	90						42	38
84	10							15
	25							23
	50							27
	75							30
	90							35
Females								
Birth	10	−10	6	18	20	21	20	19
	25	− 9	11	22	25	26	25	24
	50	11	19	28	29	29	28	26
	75	21	26	32	33	32	31	30
	90	32	31	38	37	36	34	32
8	10		15	24	24	23	21	20
	25		22	28	28	28	26	25
	50		32	34	34	33	30	27
	75		41	41	38	36	33	31
	90		47	46	42	39	37	34
14	10			25	24	23	21	20
	25			29	29	28	26	4
	50			35	34	32	30	28
	75			42	38	37	33	31
	90			49	42	39	37	34
28	10				20	21	20	20
	25				26	26	24	23
	50				31	30	28	26
	75				36	34	31	29
	90				41	39	37	34
42	10					20	19	19
	25					24	22	21
	50					29	27	25
	75					34	30	28
	90					40	35	32
56	10						18	17
	25						21	20
	50						25	23
	75						29	27
	90						34	3[illegible]
84	10							14
	25							19
	50							22
	75							26
	90							31

greater (by 286 301 and 590 g, respectively) for infants of the formula-fed series than for those of the breastfed series. At age 8 days the 10th, 50th and 90th percentile values for length were greater (by 0.3 0.4 and 1.0 cm, respectively) for formula-fed than for breast fed infants. At age 112 days, the 10th per centile values were nearly identical but the 50th and 90th percentile values were greater (by 1.0 and 0.9 cm, respectively) for formula-fed than for breastfed infants.

Gain in weight In contrast to the data previously reported (4) for breastfed infants, most formula fed infants had regained birth weight by the eighth day of life (Table 9) During the interval 8–112 days, mean gain in weight by formula-fed males was 32.6 g/day and that by formula-fed females was 27.6 g/day (Table 6) The sex-related difference in gain in weight was statistically significant ($p < 0.05$) Per centile values for gains in weight during various intervals are presented in Table 9

The mean gains in weight by formula-fed males and females during the interval 8–112 days (Table 6) were slightly greater than the corresponding values (30.7 and 26.0 g/day) for breastfed infants studied previously (4) On a sex specific basis, the differences were not statistically significant. In all age intervals, percentile values for gain in weight were

Table 10 *Daily change in length (mm/day) between selected ages*

Age (days)	Percentile	42 days	56 days	84 days	112 days
Males					
8	10	1.1	1.1	1.0	1.0
	25	1.2	1.2	1.1	1.0
	50	1.4	1.3	1.2	1.1
	75	1.5	1.4	1.3	1.2
	90	1.6	1.5	1.4	1.3
14	10		1.0	1.0	1.0
	25		1.1	1.1	1.0
	50		1.2	1.2	1.1
	75		1.3	1.2	1.2
	90		1.4	1.3	1.2
28	10			1.0	0.9
	25			1.0	1.0
	50			1.2	1.1
	75			1.2	1.1
	90			1.3	1.3
42	10			0.9	0.8
	25			1.0	0.9
	50			1.1	1.0
	75			1.2	1.1
	90			1.3	1.2
56	10				0.8
	25				0.9
	50				1.0
	75				1.1
	90				1.2
Females					
8	10	1.0	1.0	1.0	0.9
	25	1.1	1.1	1.1	1.0
	50	1.3	1.2	1.1	1.0
	75	1.4	1.3	1.2	1.1
	90	1.5	1.4	1.3	1.2
14	10		1.0	0.9	0.9
	25		1.1	1.0	1.0
	50		1.2	1.1	1.0
	75		1.2	1.1	1.1
	90		1.4	1.2	1.1
28	10			0.9	0.8
	25			0.9	0.9
	50			1.0	1.0
	75			1.1	1.0
	90			1.2	1.1
42	10			0.8	0.8
	25			0.9	0.9
	50			1.0	1.0
	75			1.1	1.0
	90			1.2	1.1
56	10				0.7
	25				0.8
	50				0.9
	75				1.0
	90				1.1

equal to or slightly greater than those by breastfed infants of the same sex Between birth and 14 days of age the 10th 50th and 90th percentile values for males fed milk-based formulas were 24 30 and 40 g/day respectively (Table 9) Corresponding values for breastfed males were 23 28 and 35 g/day Similarly the 10th, 50th and 90th percentile values for female infants fed milk-based formulas were 19 26 and 32 g/day compared with 18, 24 and 29 g/day for breastfed females. We have previously (4) called attention to the importance of specifying duration of observation when discussing percentile gains that differ substantially from the median (e.g., the 90th and 10th percentiles) The data in Table 9 provide further examples in this regard. It may be seen that the 90th percentile values for gain in weight by male infants during three successive 14-day intervals—14–28 28–42 and 42–56 days—were 54 56 and 53 g/day respectively whereas the 90th percentile value for gain in weight by the same infants for the entire 42-day interval (14–56 days) was 50 g/day Clearly many of the infants whose gain in weight was greater than the 10th percentile value in one of the 14-day intervals demonstrated gains less than the 90th percentile value in the other 14-day intervals. The 10th percentile values for gains in weight by male infants in the intervals 14–28, 28–42, and 42–56 days were 30, 29 and 22 g/day respectively whereas the 10th percentile value for the entire 42-day interval, 14–56 days, was 30 g/day

Gain in length. A relatively large percentage error in measurement must be accepted when average daily gain in length is calculated from observations made during a short interval. For example, an infant whose length was 50.0 cm at age 14 days and 52.0 cm at age 28 days demonstrated an average gain of 1.4 mm/day However if measurement of length at 14 days had been recorded as 49.8 cm and at 28 days as 52.2 cm, he would seem to have gained 1.7 mm/day If on the other hand, the measurement at age 14 days had been recorded as 50.2 cm and at age 28 days as 51.8 cm, he would seem to have gained 1.1 mm/day Because of the uncertainty regarding changes in length during relatively short intervals, we

have not presented data on gains in length (Tables 6 and 10) for intervals less than 34 days.

During the interval 8–112 days (Table 6), the mean gain in length by formula fed males was 1 12 mm/day and that by formula-fed females was 1 05 mm/day The sex related difference in gain in length was statistically significant ($p < 0.05$) These gains in length by formula-fed males and females were slightly greater than the corresponding gains (1.09 and 1.03 mm/day respectively) by breastfed males and females but the differences were not statistically significant.

In spite of the lack of statistically significant differences, the greater gains in weight and length by the formula-fed than by the breast fed infants deserve comment. It should be noted that the statistical comparison concerns those infants who completed 111 days of observation—91 % of the formula-fed series and only 70 % of the breastfed series. The breast fed infants completing 111 days of study were unquestionably a selected group It should also be noted that most of the breastfed infants received one formula feeding daily a practice that may have augmented gain in weight.

Relation of gain in weight to gain in length Between 8 and 112 days of age mean gain in weight per unit of gain in length was 29 1 g/mm (standard deviation 2.1) for males and 26.2 g/mm (S.D 1.9) for females. The difference in these mean values was statistically significant ($p < 0.05$)—an unexpected finding since we had concluded, tentatively that adipose tissue probably accounted for a larger percentage of weight gain of females than of males and had considered it likely that this difference would be reflected in greater gain in weight per unit of gain in length by females. It seems likely that if such difference in adipose tissue is present, it must be more than offset by the greater synthesis of fatfree tissue (especially bone and muscle) associated with the more rapid linear growth of males.

The sex related difference in gain in weight

Table 11 *Relation of weight gain (g) to calorie intake (kcal) during various age intervals*

Age interval (days)	Regression[a] equation	Correlation coefficient	Residual variance S^2
Males			
8–13	$Y = .058x + 8$	.36	190
14–27	$Y = .067x + 10$	.66	55
28–41	$Y = .046x + 15$	.31	70
42–55	$Y = .079x - 9$	.61	91
56–83	$Y = .062x - 6$	70	35
84–111	$Y = .044x - 1$	49	39
8–55	$Y = .069x + 4$	74	27
56–111	$Y = .054x - 4$	.67	24
8–111	$Y = .064x - 3$	77	17
Females			
8–13	$Y = .008x + 28$	.06	142
14–27	$Y = .065x + 8$	48	59
28–41	$Y = .051x + 6$	49	51
42–55	$Y = .062x - 7$	.60	43
56–83	$Y = .056x - 3$	.57	45
84–111	$Y = .039x + 7$	.39	48
8–55	$Y = .069x + 3$	.67	21
56–111	$Y = .051x - 4$	.56	22
8–111	$Y = .064x - 4$	.66	13

Y is volume of intake (ml/day) or calorie intake (kcal/day) and x is body weight (kg).

per unit of gain in length was present in the breastfed series also: 28.0 g/mm (S.D 4 1) for males and 25.3 g/mm (S.D 3.3) for females. This difference was not statistically significant.

Calorie intake and growth

Calorie intake and gain in weight Gain in weight, expressed as grams gained per 100 kcal consumed, was highly variable during the age interval 8–13 days (Table 4) a finding to be anticipated in view of the variable gains in weight during this interval. Because younger infants gain weight more rapidly and consume fewer calories than do older infants, the steady decrease in gain in weight per unit of calorie intake (Table 4) with increasing age was anticipated.

Table 11 and Fig. 4 present the relation of gain in weight to calorie intake for males and for females during the following age intervals: 8–13 14–27 28–41 42–55 56–83 and 84–111 days. Table 11 also includes the relation of

Table 10 *Daily change in length (mm/day) between selected ages*

Age (days)	Percentile	42 days	56 days	84 days	112 days
Males					
8	10	1.1	1.1	1.0	1.0
	25	1.2	1.2	1.1	1.0
	50	1.4	1.3	1.2	1.1
	75	1.5	1.4	1.3	1.2
	90	1.6	1.5	1.4	1.3
14	10		1.0	1.0	1.0
	25		1.1	1.1	1.0
	50		1.2	1.2	1.1
	75		1.3	1.2	1.2
	90		1.4	1.3	1.2
28	10			1.0	0.9
	25			1.0	1.0
	50			1.2	1.1
	75			1.2	1.1
	90			1.3	1.3
42	10			0.9	0.8
	25			1.0	0.9
	50			1.1	1.0
	75			1.2	1.1
	90			1.3	1.2
56	10				0.8
	25				0.9
	50				1.0
	75				1.1
	90				1.2
Females					
8	10	1.0	1.0	1.0	0.9
	25	1.1	1.1	1.1	1.0
	50	1.3	1.2	1.1	1.0
	75	1.4	1.3	1.2	1.1
	90	1.5	1.4	1.3	1.2
14	10		1.0	0.9	0.9
	25		1.1	1.0	1.0
	50		1.2	1.1	1.0
	75		1.2	1.1	1.1
	90		1.4	1.2	1.1
28	10			0.9	0.8
	25			0.9	0.9
	50			1.0	1.0
	75			1.1	1.0
	90			1.2	1.1
42	10			0.8	0.8
	25			0.9	0.9
	50			1.0	1.0
	75			1.1	1.0
	90			1.2	1.1
56	10				0.7
	25				0.8
	50				0.9
	75				1.0
	90				1.1

equal to or slightly greater than those by breastfed infants of the same sex. Between birth and 112 days of age the 10th, 50th and 90th percentile values for males fed milk-based formulas were 24, 30 and 40 g/day respectively (Table 9). Corresponding values for breastfed males were 23, 28 and 35 g/day. Similarly the 10th, 50th and 90th percentile values for female infants fed milk based formulas were 19, 26 and 32 g/day compared with 18, 24 and 29 g/day for breastfed females. We have previously (4) called attention to the importance of specifying duration of observation when discussing percentile gains that differ substantially from the median (e.g., the 90th and 10th percentiles). The data in Table 9 provide further examples in this regard. It may be seen that the 90th percentile values for gain in weight by male infants during three successive 14-day intervals—14–28, 28–42 and 42–56 days—were 54, 56 and 53 g/day respectively whereas the 90th percentile value for gain in weight by the same infants for the entire 42-day interval (14–56 days) was 50 g/day. Clearly many of the infants whose gain in weight was greater than the 10th percentile value in one of the 14-day intervals demonstrated gains less than the 90th percentile value in the other 14-day intervals. The 10th percentile values for gains in weight by male infants in the intervals 14–28, 28–42, and 42–56 days were 30, 29 and 22 g/day respectively whereas the 10th percentile value for the entire 42-day interval, 14–56 days, was 30 g/day.

Gain in length. A relatively large percentage error in measurement must be accepted when average daily gain in length is calculated from observations made during a short interval. For example, an infant whose length was 50.0 cm at age 14 days and 52.0 cm at age 28 days demonstrated an average gain of 1.4 mm/day. However if measurement of length at 14 days had been recorded as 49.8 cm and at 28 days as 52.2 cm, he would seem to have gained 1.7 mm/day. If on the other hand, the measurement at age 14 days had been recorded as 50.2 cm and at age 28 days as 51.8 cm he would seem to have gained 1.1 mm/day. Because of the uncertainty regarding changes in length during relatively short intervals, we

of calorie intake mean daily gain in length was greater in the age interval 8–55 days than in the age interval 56–111 days, and greater by males than by females. Mean gain in length per unit of calorie intake during the interval 8–111 days was identical (0.21 mm/100 kcal) for males and females.

DISCUSSION AND SPECULATION

As has been mentioned, data on food consumption and growth of normal infants fed nutritionally adequate formulas may be useful for several purposes. Animal studies have demonstrated that deficiency of an essential nutrient in a diet commonly leads to decreased food consumption. Thus, in studies with a newly designed formula for human infants, abnormally low food consumption (ml/day or kcal/day) in relation to age and body weight would suggest the possibility of deficiency or unavailability of an essential nutrient or perhaps, some other unsatisfactory characteristic of the formula (e.g unpalatability) Conversely excessive caloric intake per unit of gain in body weight would suggest poor digestibility of the formula with increased food consumption reflecting the attempt of the infant to achieve an adequate net" caloric intake (3). It is apparent that the distinction between normal and abnormal intake of calories or between normal and abnormal gain in weight or length or in gain in weight per unit of calorie intake requires normative data such as those presented in Tables 4–7 and 9–11 and in Figs. 2 and 4

Because food habits established in infancy may persist throughout life, knowledge of factors controlling food intake during infancy seems essential as a basis for sound recommendation concerning nutritional management of infants. We need to learn the extent to which infants fed ad libitum will increase their volume of intake to compensate for low caloric concentration of a diet and the extent to which they will decrease their volume of intake when a diet of high caloric concentration is fed. Such information is particularly necessary because commercially prepared strained foods with wide variability in caloric concentration are currently introduced into the diet during the early months of life. Data presented here (especially Tables 4 5 and 7 and Figs. 1 and 2) may be useful as a basis for comparison with similar data concerning normal infants receiving diets of relatively high or low caloric density (3) The data may also be useful in study of other dietary factors influencing satiety—a topic about which little information relative to infant feeding is available.

We believe that data presented here may be useful in the interpretation of findings relating to infants suspected of abnormality Early identification of failure to thrive presupposes a knowledge of percentile values for gain in weight and length by normal infants. Such data for the first 112 days of life are presented in Tables 9 and 10 of this report. Similarly data on food consumption (especially Table 7 and Figs. 1 and 2) and on gain in weight per unit of calorie intake (Table 11 and Fig. 4) by normal infants may be useful in evaluating the performance of infants suspected of abnormality

Of some interest was the observation that at a specified body weight, mean calorie intake was greater by younger than by older infants, presumably reflecting the greater calorie needs for growth of the more rapidly growing younger infants. The relation of calorie intake to body weight on a sex-specific basis for relatively short age intervals (Table 7 and Fig. 2) offers greater sensitivity in evaluating calorie intakes than does the relation of calorie intake per unit of body weight to age

The statistically significant relationship demonstrated in this study between gain in weight and calorie intake in various age intervals (Table 11) confirms and extends our previous observations (5) A statistically significant correlation between these variables might not be demonstrable in study of groups of subjects more heterogeneous with respect to birth weight, age, sex, diet and state of health,

or in study of older infants. In addition, other methodology (e.g., estimation of calorie intake by history) might not be sufficiently precise to demonstrate such a correlation We believe that some combination of these factors explains the failure of other investigators (12, 13) to demonstrate a statistically significant relation between gain in weight and calorie intake

Data presented here provide a basis for speculation about the relative energy partition for maintenance and growth by normal infants. In studies of infant pigs, Kotarbinski and Kielanowski (9) found the energy cost to be 7.5 kcal for synthesis of one gram of protein and 11.6 kcal for synthesis of one gram of fat. Studies of older pigs have demonstrated greater energy costs of synthesis of fat and, especially protein (1 9 14) than those reported for infant pigs. Energy costs of synthesis of protein and fat by young growing sheep (10) and rats (11) also appear to be greater than those for infant pigs. However the infant pigs studied by Kotarbinski and Kielanowski (9) were almost certainly less mature than the other animals studied and data from this source appear to be the best currently available for estimating energy costs of synthesis of protein and fat by human infants between 8 and 112 days of age

If one considers that the average composition of the weight gained by formula fed male infants between 8 and 112 days of age is similar to that of the "male reference infant" (2 b) the gain will include 11 4% protein and 40.8% lipid. Thus, each 100 g gain will require 559 kcal (11 4 g × 7.5 kcal/g + 40 8 g × 11 6 kcal/g = 559 kcal) The average daily gain of 32.6 g will therefore require 182 kcal/day

Mean daily intake of calories by males during the age interval 8–111 days was 553 kcal/day It is reasonable to assume that when vegetable oils provide the fat in infant formulas, only about 5% of calorie intake will be lost in the feces (7) Thus, average daily intake of metabolizable energy may be estimated as 525 kcal/day (553 kcal/day total intake minus an estimated fecal loss of 28 kcal/day) and energy required for maintenance is estimated to be 343 kcal/day (525 kcal/day metabolizable energy minus 182 kcal/day for growth) Thus, during this period of rapid growth, perhaps one third of total calorie intake is utilized for growth. Average body weight during the period 8–111 days may be determined by dividing calorie intake per day by calorie intake per kilogram per day (Table 4) and will be found to be 5.21 kg. Thus, calorie expenditures for maintenance may be estimated to be 66 kcal/kg/day

Speculation concerning utilization of calories for growth and maintenance during early infancy seems more useful for defining the areas of our ignorance than in providing important insights into quantitative aspects of growth and energy utilization. The observations concerning calorie intakes and gains in weight and length of individual infants we believe to be reasonably sound. However even if we felt confident that the average composition of gain from 8 to 112 days was 11 4% protein and 40.8% fat and that the average energy costs of synthesis of protein and fat were 7.5 and 11 6 kcal/g, respectively there would remain many exceedingly troublesome questions. What is the difference in composition of gain and in energy costs of tissue synthesis at different ages during this interval (e.g., 8 to 28 days versus 84 to 112 days)? What is the extent of individual variation in composition of gain? Is there a substantial difference in energy costs of synthesis of protein (or fat) by different infants of the same sex, age and size? Are there important sex-related differences in composition of gain and in energy costs of synthesis of protein (or fat)? Do average calorie needs for activities other than growth differ significantly with age and sex and, among infants of the same sex, what is the extent of variability in such calorie needs?

Answers to these questions must be found if we are to develop a sound understanding of the nature of growth and to be able to make reasonable estimates of requirements for calories and individual nutrients.

SUMMARY

Infant formulas believed to be fully adequate nutritionally were fed to normal fullterm infants from 8 to 112 days of age. Weight of each food consumed by each infant during each day of study was recorded. From the weight of food consumed and its density and caloric concentration, volume of intake (ml/day and kcal/day) and caloric intake (kcal/day and kcal/kg/day) were calculated for each of the following age intervals: 8–13, 14–27, 28–41, 42–55, 56–83 and 84–111 days. Body weight and length of each infant were determined at ages 8, 14, 28, 42, 56, 84 and 112 days.

Of the 154 infants enrolled in the study 142 (91 %) completed the planned period of observation to age 112 days. Analysis of the data is based on the 142 infants for whom complete data were available; data on all infants are presented in the appendices.

Nine formulas were fed, each supplying 67 kcal/100 ml, with protein from cow milk and fat from vegetable oils (one formula also contained butterfat). An analysis of variance on a sex specific basis for the age interval 8–111 days failed to reveal statistically significant ($p < 0.05$) feeding related differences with respect to volume of intake (ml/day), caloric intake (kcal/day), gain in weight (g/day or g gain per 100 kcal consumed) or gain in length (mm/day or mm gain per 100 kcal consumed).

Combined data for all feeding groups are summarized on a sex specific basis for various age intervals with respect to food consumption (volume of intake and intake of calories), gains in weight and length, and gains in weight per unit of food consumed. At a specified body weight, it was found that mean caloric intake was greater by younger than by older infants, an observation interpreted as reflecting greater calorie needs for growth by the more rapidly growing younger infants. The 10th, 25th, 50th, 75th and 90th percentile values for gain in weight are presented for each sex for all age intervals and the same percentile values for gain in length for all age intervals of at least 34 days duration. The regressions of volume of intake (ml/day) on body weight, caloric intake (kcal/day) on body weight, and weight gain (g/day) on caloric intake (kcal/day) are presented for the age intervals 8–13, 14–27, 28–41, 42–55, 56–83 and 84–111 days.

During the interval 8–111 days, mean values for males were greater than those for females with respect to the following: volume of intake (ml/day), intake of calories (kcal/day), gain in weight (g/day), gain in length (mm/day), and gain in weight per unit of gain in length. These sex-related differences were statistically significant ($p < 0.05$). Not statistically significant were sex related differences in gain in weight per unit of calorie intake or gain in length per unit of calorie intake.

On a sex specific basis, mean gains in weight and length during the age interval 8–112 days were greater by the formula-fed infants in the present study than by breastfed infants studied previously. These differences were not statistically significant. However, it was noted that this analysis applied to infants who remained in the study until 112 days of age—91 % of infants enrolled in the formula fed series and only 70 % of infants enrolled in the breastfed series. Clearly, the breastfed infants were a highly selected group.

The data on the formula fed infants are believed to be useful for at least three purposes: evaluation of other formulas providing 67 kcal/100 ml, study of factors influencing food consumption by normal infants, and assessment of performance of individual infants suspected of abnormality. The data also afford a basis for speculating about the partition of calories for growth and maintenance. It is estimated that during the age interval 8–111 days, perhaps one-third of caloric intake is utilized for growth.

ACKNOWLEDGEMENT

We are grateful to Dr Paul E. Leaverton for statistical advice and review of the manuscript and to Mrs Barbara Hudgins for cheerful typing of many drafts of the manuscript and for meticulous verification of the tabular data.

REFERENCES

1 Close, W H. & Mount, L. E. Energy retention in the pig at several environmental temperatures and levels of feeding. *Proc Nutr Soc 30:* 33 A, 1971

2. Fomon, S. J *Infant nutrition*. Saunders, Philadelphia, 1967 (*a*) pp. 13–14, (*b*) pp. 30–32.

3 Fomon, S. J Filer L. J Jr & Thomas, L. N Influence of caloric density and digestibility of diet on food consumption by normal infants fed ad libitum. *Proc 13th Internat Congr Pediat Vienna*, Vol. II, Nutrition and Gastroenterology 1971 p. 489

4. Fomon, S. J Filer L. J Jr., Thomas, L. N & Rogers, R. R. Growth and serum chemical values of normal breastfed infants. *Acta Paediat Scand* (Suppl. 202), 1970.

5 Fomon, S. J Filer L. J Jr Thomas, L. N Rogers, R. R. & Prolsch, A. M. Relationship between formula concentration and rate of growth of normal infants. *J Nutr 98*, 241 1969

6. Fomon, S. J Ziegler E. E., Thomas, L. N. & Filer L. J., Jr Protein requirement of normal infants between 8 and 56 days of age. In Visser H. K. A. (ed.): *Metabolic processes in the foetus and newborn infant. Nutricia Symposium* Vol. III. Stenfert Kroese Leiden, 1971

7 Fomon, S. J Ziegler E. E., Thomas, L. N Jensen, R. L. & Filer L. J Jr Excretion of fat by normal fullterm infants fed various milks and formulas. *Am J Clin Nutr 23* 1299 1970.

8. Huntsberger D V & Leaverton, P E. *Statistical inference in the biomedical sciences*. Allyn & Bacon, Inc., Boston, 1970 (*a*) p. 213, (*b*) pp. 140–144 (*c*) pp. 167 178.

9 Kotarbińska, M & Kielanowski, J. In Blaxter K. L., Kielanowski, J & Thorbek, G. (eds.): *Energy metabolism of farm animals. Proc. 4th Symp Energy Metab, Jablonna, 1967* Oriel Press, Newcastle, 1969 pp. 299–311

10. Ørskov E. R. & McDonald, I. The utilization of dietary energy for maintenance and for fat and protein deposition in young growing sheep. *Energy metabolism of farm animals. European Association for Animal Production*, Publ. No. 13 Juris Druck & Verlag, Zürich, 1970, pp. 1 1 124

11 Pratt, A. W & Pitney F K. Gross body composition and total energy metabolism in normal rats. *Amer J Physiol, 197* 660, 1959

12. Rose, H. E. & Mayer J Activity caloric intake, fat storage, and the energy balance of infants. *Pediatrics, 41* 18, 1968.

13 Rueda-Williamson, R. & Rose, H E. Growth and nutrition of infants. The influence of diet and other factors on growth. *Pediatrics, 30*, 639 1962.

14. Thorbek, G. Studies on the energy metabolism of growing pigs. In Blaxter K. L., Kielanowski, J & Thorbek, G (eds.): *Energy metabolism of farm animals. Proc 4th Symp Energy Metab Jablonna 1967* Oriel Press, Newcastle, 1969 pp. 281 289

Appendix I Weights of individual infants at various ages

Subject number	Birth weight	8 days	14 days	28 days	42 days	56 days	84 days	112 days
Males								
Formula 3215A								
950	3 910	3 797	4 044	4 784	5 566	6 066	7 019	7 979
951	3 120	3 307	3 400	3 960	4 530	5 020	5 775	6 445
952	3 760	3 955	4 164	4 891	5 472	5 932	6 754	7 532
953	3 760	3 665	3 841	4 360	4 [illegible]	5 215	6 379	7 052
954	3 420	3 578	3 775	4 410	4 835	5 255	5 850	6 285
955	3 350	3 385	3 607	4 311	4 828	5 330	6 247	6 975
956	3 460	3 600	3 806	4 497	4 867	5 336	6 345	7 016
958	3 910	3 840	4 059	4 755	5 580	6 253	7 500	8 361
960	3 230	3 380	3 583	4 387	4 892	5 599	7 013	8 013
962	3 010	2 878	3 133	3 938	4 430	4 789	5 473	5 736
963	2 860	2 940	3 130	3 641	4 520	5 255	6 555	7 450
Formula 29B								
126	3 160	3 226	3 350	3 825	4 280	4 725	5 198	6 03[illegible]
127	3 100	3 280	3 331	3 895	4 442	4 965	5 846	6 600
130	3 130	3 285	3 465	4 100	4 740	5 550	6 500	7 363
132	3 530	3 539	3 607					
133	3 350	3 420	3 566	4 032				
134	3 500	3 640	3 756	4 245				
136	3 720	4 000	4 061	4 577	5 087	5 779	6 844	7 604
137	3 380	3 545	3 654	4 209	4 618	4 950	5 538	6 [illegible]
140	4 150	3 960	4 196	4 517	5 137	5 444	6 044	6 835
145	2 550	2 577	2 765	3 361	3 989	4 521	5 304	5 880
149	3 800	3 850	4 034	4 460	4 874	5 178	5 838	6 525
150	2 550	2 655	2 762	3 260	3 656	4 245	5 182	5 932
153	2 860	2 835	3 155	3 760	4 390	5 122	5 724	6 510
Formula 5024A								
1350	3 480	3 545	3 575	4 235	4 620	5 050	5 850	6 744
1352	2 980	2 930	3 170	3 705	4 315	5 228	6 494	7 518
1353	3 890	3 861	4 137	4 911	5 575	6 342	7 197	8 129
1354	3 130	3 248	3 416	3 945	4 409	4 912	5 788	6 630
1355	3 400	3 502	3 634	4 170	4 661	5 066	5 930	6 756
1356	3 270	3 248	3 665	4 689	5 675	6 493	7 690	8 851
1357	3 320	3 474	3 614	4 231	4 758	5 144	5 856	6 242
1358	3 720	3 698	3 766	4 177	4 536	4 897	5 329	5 966
1359	3 620	3 761	3 969	4 668	5 173	5 716	6 578	7 251
1360	3 800	3 670	3 766	3 981	4 410	4 895	5 711	6 461
1361	2 785	2 707	2 860	3 350	3 775	4 255	5 209	5 919
1362	3 010	3 635	4 014	4 842	5 288	5 482	6 236	7 212
1363	2 870	2 800	2 975	3 555	3 915	4 275	5 130	5 770
1364	3 230	3 307	3 545	4 037	4 550	5 600	6 154	6 925
Formula 3221A								
1401	3 570	3 512	3 849	4 425	5 145	5 885	6 779	7 607
1402	3 760	3 873	3 962	4 539	5 033	5 488	6 518	7 256
1403	3 620	3 589	3 665	4 165	4 620	4 950	5 485	6 172
1404	3 120	3 137	3 317	4 169	4 774	5 326	6 365	7 246
1405	3 640	3 585	3 815	4 437	5 249	5 909	7 358	8 223
1406	3 545	3 490	3 773	4 454	5 162	5 807	6 666	7 576
1407	3 800	3 979	4 136	4 770	5 413	5 827	6 377	7 051
1408	3 380	3 303	3 765	4 215	4 840	5 335	6 311	6 446
1409	3 580	3 703	3 920	4 350	4 855	5 150	5 756	6 389
1410	3 150	3 205	3 430	4 078	4 474	4 826	5 482	6 099
1411	3 560	3 560	3 737	4 256	4 867	5 343	6 242	7 072
1412	2 930	2 877	3 036	3 615	4 205	4 742	5 697	6 486
1413	3 930	4 057	4 397	5 091	5 516	5 791	5 303	6 697
1414	3 240	3 320	3 456	4 139	4 612	5 054	5 946	6 531
1415	3 470	3 625	3 785	4 225	4 710	5 020	5 600	6 025

Appendix I (*continued*)

Subject number	Birth weight	8 days	14 days	28 days	42 days	56 days	84 days	11 days
Formula 3215E								
1201	870	3 029	3 285	3 628	4 043	4 539	5 114	5 782
1202	3 810	3 901	4 095	4 715	5 3[illegible]1	5 700		
1203	3 260	3 211	3 397	3 938	4 446	4 934	5 860	6 604
1204	3 590	3 828	3 899	4 657	5 215	6 055	7 220	8 226
1205	3 740	3 579	3 720	4 450	4 975	5 410	6 310	6 700
1206	3 440	3 475	3 632	4 053	4 565	5 175	6 108	7 033
1207	4 090	4 056	4 131	4 554	5 072	5 292	5 892	6 208
1208	3 100	3 075	3 183	3 66[illegible]	4 323	4 6[illegible]6	5 273	5 961
1209	3 200	3 400	3 547	4 263	4 983	5 308	5 928	6 531
1[illegible]10	3 465	3 779	3 946	4 481	5 055	5 613	6 135	6 874
1211	3 410	3 480	3 699	4 [illegible]48	4 856	5 320	6 366	7 171
121[illegible]	3 090	3 [illegible]88	3 3[illegible]5	3 982	4 498	4 998	5 825	6 403
1[illegible]13	3 380	3 285	3 493	4 085	4 670	5 066	5 803	6 553
1214	3 520	3 649	3 814	4 302	4 [illegible]83	5 258	5 973	6 696
1215	3 690	3 650	3 854	4 4[illegible]6	5 228	5 744	6 744	7 726
1216	3 780	3 677	3 772	4 335	4 915	5 185	5 800	6 325
Females								
Formula 3[illegible]15A								
975	4 540	4 400	4 507	4 817	4 954	5 269	5 664	5 900
976	3 540	3 670	3 835	4 360	4 824	5 188	5 930	6 370
977	4 020	4 275	4 448	4 948	5 308	5 686	6 224	6 766
978	3 430	3 710	3 890	4 317	4 820	5 [illegible]89	6 005	6 705
979	3 100	3 [illegible]89	3 422	3 793	4 227	4 528	5 309	5 845
980	3 [illegible]40	3 775	3 472	3 935	4 603	5 110	6 067	6 839
981	3 295	3 350	3 551	4 067	4 492	4 951	5 974	6 638
982	730	814	2 975	3 275	3 668	4 134	5 102	5 637
983	3 370	3 3[illegible]5	3 465	3 915	4 314	4 772	5 595	5 908
984	3 [illegible]20	3 297	3 510	4 135	4 710	5 310	6 065	6 583
985	3 420	3 385	3 560	4 026	4 547	4 899	5 7[illegible]4	6 413
986	2 740	2 820	3 031	3 483	3 924			
987	3 360	3 481	3 754	4 489	5 087	5 672	6 621	7 491
988	2 780	2 905	3 121	3 760	4 374	4 976	5 916	6 554
989	3 240	3 345	3 631	4 168	4 682	4 960	5 526	6 325
990	2 910	2 913	3 125	3 527	3 793	4 197	4 987	5 519
Formula 29B								
135	3 180	3 130	3 252	3 665	4 091	4 473	5 218	5 959
139	3 180	3 295	3 507	3 957	4 438	4 862	5 576	5 993
143	3 600	3 600	3 817	4 387	4 725	5 4[illegible]	5 927	6 530
144	3 680	3 796	4 015	4 560	5 000	5 435	6 195	6 950
147	3 290	3 340	3 430	3 888	4 373	4 818	5 411	6 152
148	3 900	3 785	4 031	4 540	5 009	5 413	6 1[illegible]3	6 513
151	3 540	3 530	3 655	4 125	4 358	4 604	4 986	5 339
152	4 080	4 080	4 208	4 558	4 673	4 903	5 388	5 858
Formula 5018C								
13[illegible]5	3 370	3 593	3 745	4 410	4 975	5 600	6 280	
1326	3 130	3 085	3 344	3 737	4 277	4 706	5 796	6 833
1327	3 940	3 964	4 165	4 699	5 036	5 375	5 989	6 009
1328	2 800	2 841	2 997	3 486	3 945	4 482	5 215	5 784
1330	3 280	3 455	3 537	3 899	4 101	4 451	5 034	5 375
1332	3 510	3 508	3 654	4 133	4 514	4 857	5 530	6 121
1333	2 560	2 600	2 827	3 392	3 842	4 313	5 084	5 777
1334	2 920	3 130	3 214	3 750	4 273	4 578	5 517	6 190
1335	3 860	3 672	3 835	4 430	4 932	5 466	6 205	7 014
1336	4 080	3 945	4 097	4 580	4 920	5 285	5 945	6 497
1337	2 890	2 980	3 245	3 689	4 121	4 503	4 845	5 809
1338	3 385	3 390	3 437	3 756	4 041	4 233	4 820	5 440
1339	3 260	2 897	3 248	3 777	4 298	4 850	5 783	6 354

Appendix I (*continued*)

Subject number	Birth weight	8 days	14 days	28 days	42 days	56 days	84 day	112 days
Formula Similac								
1375	2 620	2 800	3 104	3 611	4 070	4 455	5 415	6 399
1376	3 360	3 272	3 461	4 135	4 561	4 920	5 569	6 214
1377	3 240	3 315	3 520	4 132	4 655	5 026	5 675	6 054
1378	2 820	2 794	2 946	3 327	3 698	4 103	4 766	6 300
1379	2 470	2 629	2 900	3 580	3 960	4 429	5 136	5 643
1380	3 540	3 430	3 645	4 380	5 035	5 622	6 654	7 610
1381	3 050	3 278	3 485	3 800	4 188	4 578	5 389	6 215
1382	2 910	3 052	3 175	3 625	4 152	4 710	5 580	6 285
1383	3 000	3 355	3 540	3 923	4 300	4 633	5 187	5 667
1384	3 110	3 250[a]		4 125	4 575	4 990	5 778	6 436
1385	3 180	3 377	3 505	3 994	4 537	4 925	5 520	6 381
1386	3 500	3 655	3 885	4 486	5 070	5 471	6 355	7 043
1387	3 750	3 699	3 831	4 412	5 025	5 545	6 419	7 086
1388	3 140	3 395	3 701	4 365	4 689	5 240	5 933	6 689
1389	3 320	3 440	3 539	3 826	4 230	4 444	4 977	5 400
Formula Formil								
451	3 170	3 310	3 594	4 087	4 573	4 883	5 478	6 059
452	4 090	4 041	4 235	4 789	5 107	5 407		
453	3 190	3 276	3 462					
454	3 865	4 055	4 100	4 497	5 014	5 499	6 184	6 812
455	4 040	4 185	4 342	4 693	5 083	5 503	6 050	6 900
456	4 130	4 215	4 458	4 756	5 255	5 578	6 107	6 650
457	3 170	3 435	3 580	4 260	4 765	5 135	5 675	6 230
458	3 000	3 194	3 381	4 060	4 460	4 946	5 680	6 345
459	2 770	3 064	3 301	4 082	4 351	4 824	5 387	6 048
460	3 700	4 020	4 111	4 692	5 155	5 691	6 361	7 026
461	2 830	3 000	3 194	3 572	3 974	4 306	4 999	5 554
462	3 620	3 880	3 966	4 367	4 751	5 199	5 953	6 526
463	3 430	3 655	3 919	4 526	4 801	5 485	6 404	6 957
464	3 420	3 507	3 777	4 511	5 071	5 369	6 562	7 183
465	3 740	3 665	3 897	4 416	4 854	5 278	5 834	6 162
466	3 610	3 697	3 735	4 405	4 900	5 400	6 050	6 600
468	2 890	3 190	3 294	3 922	4 511			
469	4 190	4 210	4 415	4 735	5 098	5 959	6 786	7 785
Formula Modilac								
1421	3 580	3 763	4 065	4 450	4 885	5 211	5 785	6 336
1422	3 300	3 503	3 583	4 203	4 728	5 021	5 998	6 622
1423	3 420	3 511	3 775	4 305	4 690	5 000	5 628	6 035
1424	3 340	3 330	3 520	4 105	4 496	4 929	5 807	6 518
1425	3 060	3 101	3 204	3 676	3 935	4 323	4 907	
1426	3 620	3 710	4 000	4 565	5 020	5 305	5 773	6 332
1427	3 360	3 287	3 570	4 258	4 920	5 355	6 400	7 193
1428	3 510	3 455	3 488	3 953	4 297	4 569	5 087	5 858
1429	2 590	2 707	2 916	3 353	3 822	4 270	5 004	5 467
1430	3 340	3 463	3 710	4 214	4 561	5 060	5 759	6 245
1431	3 320	3 408	3 525	3 880	4 208	4 600	5 000	5 572
1432	2 970	3 052	3 176	3 822	4 218	4 602	5 423	6 050
1433	4 160	4 135	4 313	4 624	4 910	5 186	5 670	6 127
1434	3 540	3 659	3 810	4 215	4 585	4 810	5 584	6 256
1435	3 640	3 735	4 000	4 365	4 633	4 954	5 573	6 126

[a] Uninterpolated value, age 7 days.

Appendix II Lengths of individual infants at various ages

Subject number	Birth date	8 days	14 days	28 days	4[illegible] days	56 days	84 days	112 days
Males								
Formula 3[illegible]15A								
950	2/17/68	51.7	52.6	55.0	56.[illegible]	57.6	60.6	63.7
951	2/23/68	48.[illegible]	49.1	50.9	52.6	54.1	57.1	60.2
952	3/23/68	55.2	55.9	58.0	60.6	62.2	64.6	66.6
953	3/25/68	54.1	55.7	56.6	58.3	60.6	63.4	65.7
954	4/5/68	51.8	53.0	54.7	57.1	58.2	61.4	63.8
955	4/3/68	51.8	52.7	54.9	56.4	57.8	61.3	64.2
956	4/8/68	52.3	52.9	54.8	56.8	58.5	62.1	65.3
958	4/25/68	53.1	54.1	55.8	57.7	59.0	62.5	65.7
960	5/12/68	52.1	52.8	54.8	57.0	58.7	62.0	63.7
96[illegible]	5/21/68	49.5	50.8	52.9	54.8	56.5	59.7	61.5
963	6/7/68	49.5	50.9	52.8	54.8	56.4	60.7	62.9
Formula 29B								
126	1/10/66	50.2	51.2	52.6	54.8	56.2	58.8	61.0
127	2/10/66	50.8	50.9	53.0	55.3	56.8	60.0	62.3
130	5/6/66	49.1	50.1	51.5	53.5	55.7	58.1	61.1
13[illegible]	5/22/66	51.4	52.4					
133	6/20/66	50.7	51.3	52.3				
134	7/25/66	53.2	54.2	56.3				
136	8/2/66	52.4	53.4	55.4	57.3	58.4	60.8	63.2
137	8/3/66	52.3	53.8	55.0	56.5	57.9	60.8	62.3
140	9/5/66	53.8	55.5	56.3	58.3	59.7	62.6	65.4
145	9/27/66	47.5	48.4	50.0	52.3	54.1	56.9	59.9
149	10/11/66	52.7	53.3	55.2	56.4	57.6	60.4	6[illegible].3
150	10/17/66	48.8	49.9	51.7	52.7	54.1	57.1	59.8
153	11/[illegible]4/66	49.2	50.2	5[illegible].2	54.6	56.0	59.0	61.4
Formula 50[illegible]4A								
1350	8/6/69	52.5	53.4	55.2	56.5	58.1	60.9	63.4
1352	9/15/69	49.8	51.0	52.7	54.8	57.6	61.6	64.4
1353	9/[illegible]4/69	51.8	53.4	55.4	57.1	59.1	6[illegible]	64.7
1354	10/4/69	50.8	51.8	54.0	56.1	57.5	60.9	6[illegible].4
1355	10/22/69	52.7	53.4	55.1	57.6	59.3	61.7	64.5
1356	10/29/69	51.7	53.1	55.6	57.7	59.3	62.7	66.0
1357	10/30/69	52.7	54.0	55.4	57.[illegible]	58.5	61.4	64.0
1358	11/8/69	50.2	50.8	52.8	53.7	54.7	57.6	60.0
1359	11/8/69	51.9	53.1	55.4	56.6	58.3	60.5	63.3
1360	11/9/69	53.9	54.0	56.3	57.3	59.5	62.7	66.0
1361	11/10/69	47.9	47.9	49.7	51.6	53.2	55.3	58.6
1362	11/16/69	52.3	54.0	55.7	57.7	59.1	61.4	64.7
1363	11/17/69	48.3	49.6	51.0	53.0	54.0	57.9	59.5
1364	11/28/69	50.3	51.8	53.7	55.9	57.5	60.8	62.7
Formula 3221A								
1401	12/3/69	51.5	52.8	55.0	56.4	58.7	62.[illegible]	65.3
1402	12/7/69	50.4	51.8	53.3	55.2	56.6	60.1	61.9
1403	1[illegible]/5/69	50.4	51.6	53.3	55.1	56.9	59.7	61.4
1404	12/11/69	49.4	50.5	52.7	54.8	55.8	59.2	61.8
1405	1[illegible]/14/69	50.6	51.8	53.0	54.8	55.9	60.2	63.5
1406	12/14/69	52.2	52.9	55.3	57.0	58.3	61.6	65.1
1407	12/20/69	52.4	53.8	55.6	57.4	59.1	61.8	62.9
1408	1[illegible]/[illegible]5/69	50.8	52.0	53.9	55.3	56.9	60.9	63.8
1409	1[illegible]/[illegible]4/69	51.2	52.1	53.4	55.7	57.0	59.4	62.4
1410	12/[illegible]3/69	49.2	51.0	52.5	54.0	55.7	58.1	60.1
1411	1[illegible]8/69	51.6	52.1	54.3	56.1	57.5	60.9	63.8
1412	1[illegible]70	48.2	49.4	51.6	53.8	54.8	58.0	61.2
1413	1/10/70	53.5	54.9	55.9	58.3	59.1	61.3	62.7
1414	1/10/[illegible]0	53.0	53.8	55.9	57.6	59.5	62.6	65.5
1415	1/14/70	52.1	52.9	53.9	56.3	57.3	60.1	62.9

Appendix II (*continued*)

Subject number	Birth date	8 days	14 day	28 days	42 days	56 days	84 days	112 days
Formula 3215E								
1201	6/18/68	48.8	50.4	51.9	52.5	54 1	57.9	60.1
1202	6/22/68	51.6	53.0	54.2	56.0	57.2		
1203	6/22/68	49.9	50.7	52.7	53.9	55.9	58.5	61 4
1204	6/25/68	51.5	51.9	54.6	57.4	58.8	61.5	64.8
1205	6/28/68	52.8	52.8	54.8	56.2	57.5	59.9	63.0
1206	7/6/68	52.7	54.2	55.2	57.8	58.6	62.0	65.2
1207	7/9/68	53.4	53.9	56.2	58.7	58.6	61 1	63.6
1208	7/21/68	49.5	49.6	51.5	53.0	54 4	57 4	59.8
1209	8/8/68	50.8	51 1	53.0	54.6	57.0	59.8	61 4
1210	8/12/68	51 4	51.6	53.5	56.2	56.9	59.2	61.9
1211	8/11/68	52 8	53.1	54.9	57.5	59 4	61.9	64.0
1212	8/21/68	51.2	52.0	53.3	55 7	57.5	60.1	62.0
1213	9/29/68	52.4	54.3	55.2	57.3	58.7	62.8	65.3
1214	10/7/68	51 7	53.4	54.7	56.5	57 7	60.8	63.2
1215	10/22/68	53.2	53.7	55.3	56.7	57.9	61.6	64.5
1216	10/25/68	51.5	52.3	54.2	55.0	56.8	60.2	61.8
Females								
Formula 3215A								
975	3/13/68	53.9	54.8	56.1	56.8	58.2	59 7	62.9
976	3/17/68	51.8	53.0	54.6	56.1	58.4	59.6	62.3
977	5/6/68	54.2	54.8	56.8	58.2	59.6	61.6	62.9
978	5/12/68	51 7	52.5	55.0	55 4	57.2	60.3	62.1
979	5 /11/68	50.7	51.8	53.0	55.1	56.6	59.2	61.5
980	5/12/68	50.2	50.7	52.9	54.3	55 7	58.4	61.2
981	6/3/68	50 8	51 7	53 6	55.2	56.5	59.2	62.4
982	8/10/68	48.0	49 1	50.1	52.1	53.1	55.5	57 1
983	8/7/68	51 4	51 7	53.8	54.7	56.1	59.5	61.6
984	9/13/68	49.5	51.0	52.2	54.0	55.6	58.3	60.3
985	9/15/68	52.1	51.9	54.0	54.8	57 1	59 4	61.6
986	9/24/68	49.2	50.0	51.6	53.0			
987	9/25/68	50.9	51 4	52.9	55.2	56.3	59.6	62.3
988	9/30/68	47.8	49 4	51 7	53.6	54.6	57.9	60.9
989	10/15/68	49.8	50.8	53.6	55.3	56.9	59.3	61 7
990	10/14/68	48.9	49 4	51.0	52.6	53 8	56.5	59.2
Formula 29B								
135	8/2/66	49.3	51 0	53.1	54.5	55.2	57 7	60.2
139	8/9/66	51.8	53.1	55.6	56.2	58.1	61.9	64.3
143	9/8/66	51.9	53.0	54.9	55.9	57.1	59 7	62.4
144	9/23/66	51 7	52.2	54.0	55.8	57 7	60.9	64.1
147	10/8/66	50.7	51.2	52.2	53.6	55.1	57 7	59.9
148	10/11/66	52.3	53 3	55.8	56.5	58.1	60.9	62.0
151	10/18/66	49.4	50.0	52.5	53 1	54 1	55.9	58.5
152	10/20/66	51.8	52.5	54.2	55.2	56.6	58.9	61 1
Formula 5018C								
1325	2/26/69	52.2	52.8	54 8	56.2	57 7	60.5	
1326	3/2/69	50 6	52.7	53 7	55.1	57.5	60 0	63.5
1327	4/3/69	54.0	54.6	56.7	57.9	59 4	62.6	63.8
1328	4/7/69	49.9	50 6	52.2	53.6	54.9	58.6	60.4
1330	8/5/69	51.5	52.3	53.9	54 7	55.7	58 0	60.8
1332	8/13/69	51.0	52 0	53.1	54 4	57.2	59.0	61.5
1333	9/7/69	46 9	48 1	50 0	52.1	52.7	54.9	58.3
1334	9/14/69	50.4	51.6	53 4	55.6	57.2	60.2	62.8
1335	9/17/69	51.5	52 6	54.9	56.6	58.4	61.2	63.6
1336	10/2/69	53.2	54.8	56.7	58.4	60.2	61 7	65.1
1337	10/2/69	48.4	49 4	51 6	53.0	54.6	57.0	59.6
1338	10/6/69	50 0	50.8	52.0	54.1	55.8	58.6	60.7
1339	10/13/69	50.5	51 6	53 1	54 7	56.3	59.2	62 5

Appendix II (*continued*)

Subject number	Birth date	8 days	14 days	28 days	42 days	56 days	84 days	112 days
Formula-Similac								
1375	10/23 69	48.6	49.8	51.2	52.8	54.5	56.7	59.6
1376	10/27/69	51.2	52.3	54.3	57 4	58.1	60.4	63 0
1377	10.31 69	49.8	51.9	52.1	54.2	55.6	58.2	60.5
1378	11/4 69	47.6	48.3	50.3	52.3	54.3	56.5	60.3
1379	11/10 69	48.3	49.2	51.6	52.3	54.2	57 1	59 6
1380	11/10,69	50.9	52.3	54.5	55.7	57 7	60.3	64.2
1381	11/22,69	51.0	52.1	53.4	55.1	55.6	58.8	61.6
1382	11/21 69	49.0	49.3	51.2	53.1	55 1	58.4	60.2
1383	11/30,69	50.2	50.2	52.5	53 1	55.1	57.5	58.7
1384	12 8 69	50.2		53.2	54.4	55.9	59 6	61.9
1385	12/18,69	50.8	51.6	52.6	54 4	56.5	59.2	61.5
1386	12/14,69	52.6	53.9	56.0	58.0	59.5	61 9	64.2
1387	12/30,69	52.7	54.1	56.0	57.0	59.2	61.2	64.0
1388	12/30,69	51 4	[illegible]	54 4	56.0	57.2	60 6	63.1
1389	12/29 69	49 9	50.6	52.0	53.5	55.1	57 8	60.1
Formula-Formil								
451	11/12,66	50.3	51 7	53.0	54.8	56.0	58.4	61 7
452	11/16,66	51.2	54 4	56.3	57 4	58.6		
453	11/17 66	49 4	51 6					
454	12,6,66	53.1	53.9	56.7	57.8	57.8	61.8	63.9
455	12/25 66	53.2	54.6	56.0	57 6	59.3	61 7	63.9
456	1/4,67	53.2	54.1	55 4	56.9	58.5	60.4	62.4
457	1/6,67	50.2	50.6	53.0	53.7	55.3	59 1	59.9
458	1/18,67	49 4	50.5	52.7	54 4	55.4	57.9	60.2
459	1/18,67	48.9	49 7	51.9	52.4	54.9	57 7	59.9
460	1/19 67	52.9	54 1	55.5	57.6	59.9	62.3	63.8
461	1/31/67	49.0	50.2	52.0	53.0	54.8	57.2	59 7
462	2/8,67	52.2	52.3	54.3	56.6	57 7	60.0	62.3
463	2/19 67	52.2	53 7	55.2	56.5	57.3	60.8	63.4
464	2/25 67	51.0	51.9	53.9	55.7	57 1	60.0	62.4
465	3/2,67	51.5	52.9	54.4	55.8	57.6	59.5	61.8
466	3/10 67	52.8	53.6	55.2	55.8	58.6	61.2	63.1
468	4/12,67	50.0	50.9	53.1	55.1			
469	4/19 67	54.8	56.2	58.0	59 6	61.5	64.0	67 1
Formula Modilac								
1421	1/7/70	51 7	53.2	55.3	56.9	58.6	61.2	63.5
1422	1/10/70	51 1	52.5	54.3	56.7	58.4	61.5	63.8
1423	1/9/70	50.4	52.0	53.2	55.1	57.5	58.5	60.8
1424	1/18/70	50.8	51 7	53.8	54 7	56.2	59.0	62.4
1425	1/26/70	50.7	51.3	52.7	54.4	55.8	58.6	
1426	1/28/70	51 7	54.0	56.5	57 7	58.9	61 7	64.5
1427	2/6/70	50.8	51.6	53.9	55.7	56.7	59.5	61.0
1428	3/4/70	50.2	51.9	53.0	55.1	56.0	59 4	62.1
1429	3/3/70	47 1	48.0	50.2	51.5	53.1	56.2	58.7
1430	3/11/70	51.3	52.2	54 4	55.6	57.2	59.8	62.9
1431	3/13/70	51.0	52.2	53.8	55 6	56.7	59.6	61 7
1432	3/31/70	48.7	50.2	50.8	53.3	54.9	56.9	59 4
1433	4/21/70	53.8	54.5	56.3	57 4	59.2	61.9	63 4
1434	4/22/70	53.0	53.9	55.9	57.8	58.4	62.2	64 7
1435	4/27/70	51.8	53.0	54.0	56.2	57.8	60.4	62.4

Appendix III Average daily weight (g) of formula consumed by individual infants during successive age intervals

Subject number	Age interval (days) 8–13	14–27	28–41	42–55	56–83	84–111
Males						
Formula 3215A						
950	701	79	674	545	686	734
951	687	737	660	782	749	778
952	526	703	829	861	835	799
953	502	728	678	793	792	844
954	635	737	843[a]	801	809	733
955	824	678	849	835	813	764
956	721	774	908	885	954	869
958	1 160	1 060	977	957	951	848
960	759	1 016	1 231	1 259	1 347	1 169
962	630	739	654	709	587	649
963	754	754	968	1 091	960	1 014
Formula 29B						
126	502	681	683	717	760	854
127	569	731	774	858	845	875
130	631	837	930	1 032	933	876
132	479	—	—	—	—	—
133	699	777	—	—	—	—
134	605	589	—	—	—	—
136	549	758	889	910	891	963
137	621	689	772	756	783	980
140	497	650	654	690	653	659
145	455	642	754	861	802	814
149	587	692	782	699	872	1 003
150	460	596	636	683	852	833
151	377	664	733	762	846	922
Formula 5024A						
1350	569	724	674	782	780	815
1352	552	699	938	946	823	903
1353	660	860	1 057	1 002	930	979
1354	520	668	765	917	959	879
1355	905	665	804	812	910	911
1356	923	1 466	1 230	1 188	1 118	1 149
1357	466	667	881	821	873	780
1358	393	521	560	605	582	561
1359	725	873	1 018	971	1 015	1 000
1360	436	556	678	854	851	924
1361	423	521	560	757	700	838
1362	726	933	986	971	900	951
1363	519	715	828	798	852	757
1364	667	675	763	834	945	921
Formula 3221A						
1401	666	724	827	893	906	870
1402	610	715	64_	777	714	709
1403	512	639	739	711	632	586
1404	680	823	805	895	808	739
1405	618	778	1 024	1 133	1 045	1 030
1406	621	857	858	892	765	824
1407	808	847	782	674	562	738
1408	743	938	877	949	912	844
1409	608	690	767	761	758	800
1410	318	706	720	607	663	865
1411	627	673	811	751	812	802
1412	346	456	544	588	661	726
1413	765	911	816	819	830	788

(*Continued*)

Subject number	Age interval (days) 8–13	14–27	28–41	42–55	56–83	84–111
1414	529	719	768	598	685	641
1415	527	655	714	743	682	639
Formula 3215E						
1201	460	550	461	607	619	634
1202	658	632	732	840	—	—
1203	591	671	662	752	763	759
1204	754	730	799	967	1 022	989
1205	588	604	699	730	845	767
1206	359	499	636	834	827	814
1207	537	584	58_	698	638	718
1208	579	657	726	698	701	741
1209	759	801	888	811	717	760
1210	759	815	821	778	767	847
1211	782	778	834	769	857	953
1212	640	744	73	756	798	725
1213	499	701	636	774	757	738
1214	570	657	774	745	803	906
1215	512	799	770	805	732	758
1216	467	554	470	610	646	60_
Females						
Formula 3215A						
975	570	460	537	551	752	655
976	470	443	749	726	814	909
977	768	766	794	778	682	747
978	792	583	743	756	708	831
979	704	676	605	685	707	742
980	782	672	598	831	757	839
981	436	641	769	733	80_	929
982	554	612	562	633	735	—
983	621	658	714	779	811	659
984	574	745	748	932	725	656
985	460	585	656	712	639	635
986	555	608	740	—	—	—
987	460	718	909	948	903	847
988	677	697	669	649	759	702
989	693	715	777	812	634	727
990	541	525	585	663	720	734
Formula 29B						
135	370	546	579	667	723	710
139	536	729	767	806	706	685
143	555	715	685	715	719	873
144	564	660	816	808	934	950
147	479	664	701	715	731	858
148	517	669	581	601	641	630
151	573	699	494	518	585	752
152	484	569	457	526	739	732
Formula 5018C						
1325	630	759	808	866	896	—
1326	408	523	663	771	827	849
1327	723	742	774	691	761	751
1328	400	584	686	711	650	677
1330	481	560	599	630	653	649
1332	679	707	673	685	670	718
1333	580	629	687	624	652	635
1334	606	679	762	725	791	801
1335	509	629	756	828	776	808
1336	423	650	1 098	738	746	771
1337	425	674	685	813	797	761

Appendix III (*continued*)

Subject number	Age interval (days)					
	8–13	14–27	28–41	42–55	56–83	84–111
1338	380	440	460	414	582	604
1339	568	670	710	755	728	683
Simulac						
1375	503	64	747	785	904	980
1376	689	808	860	820	832	888
1377	460	689	863	788	841	730
1378	560	541	679	759	799	703
1379	589	778	800	844	742	572
1380	719	843	973	1 003	977	988
1381	709	701	838	716	809	890
1382	526	604	807	745	932	910
1383	606	831	1 002	742	756	837
1384	654	690	671	685	719	708
1385	710	711	881	910	796	931
1386	573	830	799	866	850	818
1387	543	685	898	845	934	970
1388	713	809	784	748	689	765
1389	563	634	459	390	604	651
Formula Formil						
451	766	780	68	730	635	613
452	6[illegible]4	692	705	631	—	—
453[a]	—	—	—	—	—	—
454	826	638	690	868	868	854[a]
455	506	553	586	726	629[a]	613[a]
456	317	520	70[illegible]	629	718	655
457	653	758	709	592	495	556
458	615	674	673	643	580	696
459	757	72[illegible]	624	600	589	704
460	785	730	689	671	683	684
461	502	531	559	578	505	510
462	535	584	715	711	770	790
463	629	746	584	778	748	810
464	486	509	746	720	815	790
465	601	713	690	705	674	563
466	601	616	688	703	737	817

(*Continued*)

Subject number	Age interval (days)					
	8–13	14–27	28–41	42–55	56–83	84–111
468	558	634	682	—	—	—
469	662	680	740	924	964	1 008
Formula Modilac						
1421	847	741	796	624	640	762
14[illegible]2	568	674	625	647	735	845
1423	758	606	575	561	665	684
1424	870	904	739	779	768	847
14[illegible]5	762	672	637	665	563	—
14[illegible]6	418	763	728	636	663	781
1427	651	780	884	792	957	974
1428	440	476	670	511	674	791
1429	430	466	537	644	717	722
1430	603	736	720	677	768	757
1431	619	537	318	537	605	744
143	653	622	795	720	700	1 127
1433	640	635	602	520	646	685
1434	588	702	656	548	562	559
1435	464	695	6[illegible]4	596	643	700

As discussed in the text (see Results and comments), one infant (Subject 954) received Karo syrup (average [illegible]g/day during the age interval [illegible]8–41 days), one infant (Subject 1362) received Lytren, a solution of glucose and electrolytes providing 28 kcal/100 ml (average 223 ml/day) during the age interval 4[illegible]–55 days), and three infants received skim milk. daily intake by Subject 454 averaged 107 ml/day in the interval 84–111 days daily intake by Subject 455 averaged 64 and 16 ml/day respectively in the age intervals 55–83 and 84–111 days, daily intake by Subject 1422 averaged 51 ml/day in the interval 4[illegible]–55 days. These intakes of Karo syrup, Lytren and skim milk are in addition to the quantities of formula tabulated in this Appendix.

[a] Formula intake in the age interval 8–13 day could not be estimated because of vomiting.

Appendix IV Average daily weight (g) of strained foods consumed by individual infants
Foods permitted according to the study protocol

Subject number	Oatmeal with bananas and applesauce 28–41	42–55	56–83	84–111	Pears 56–83	84–111	Applesauce 84–111	Bananas 84–111
Males								
Formula 3215A								
950	42	81	126	188	72	36	36	51
951	—[b]	—	15	41	47	65	6	36
952	30	29	58	143	40	29	20	15
953	—	—	43	21	47	23	15	1
954	18	10	10	11	11	4	6	—
955	39	65	8	41	36	16	7	32
956	—	—	—	26	—	5	—	5
958	39	128	70	46	39	25	42	29
960	—	—	—	—	—	—	—	—
962	—	29	3	10	5	22	5	16
963	—	—	—	—	—	—	—	—
Formula 29B								
126	28	28	28	24	10	10	—	12
127	7	65	34	19	14	19	19	5
130	41	16	20	19	—	24	28	4
132								
133								
134								
136	34	39	23	12	21	14	19	11
137	—	—	—	—	—	—	—	—
140	—	18	30	9	—	—	—	9
145	16	35	9	18	6	16	7	15
149	—	—	—	42	—	18	—	—
150	—	16	3	—	18	23	4	5
153	48	84	123	69	62	4	5	47
Formula 5024A								
1350	—	—	10	55	11	44	6	33
1352	321	141	325	160	16	6	—	—
1353	10	42	28	36	28	46	11	5
1354	16	9	21	97	8	27	10	16
1355	—	—	25[a]	36[a]	—	6	11	—
1356	34	23	25	5	23	5	—	—
1357	20	66	13	16	27	32	26	26
1358	45	100	60	92	34	32	—	21
1359	—	28	39	21	28	11	15	—
1360	12	178	55	98	33	27	—	5
1361	46	22	24	17	18	9	9	10
1362	—	23	5	11	15	16	30	16
1363	—	—	—	32	—	5	—	—
1364	40	91	60	65[a]	—	5	5	—
Formula 3221A								
1401	115	19	22	—	11	—	14	21
1402	—	—	67	37	96	19	22	25
1403	21	56[c]	56[c]	50[a]	5	31	11	17
1404	11	—	30	32	29	42	12	4
1405	4	6	16	12	5	—	10	17
1406	10	—	—	—	—	3	4	4
1407	93	86	129	128	48	29	—	121
1408	39	57	87	70	106	42	38	24
1409	28	21	27	51	47	22	26	26
1410	35	—	—	6[a]	22	28	11	22

All or part of the cereal was Rice Cereal with Applesauce and Bananas.
A dash indicates that the infant did not consume the designated food in that age interval; absence of any entry indicates that the infant was no longer in the study during that age interval.
All or part of the cereal was Mixed Cereal with Applesauce and Bananas.

Appendix IV (*continued*)

Subject number	Oatmeal with bananas and applesauce				Pears		Applesauce	Bananas
	28–41	42–55	56–83	84–111	56–83	84–111	84–111	84–111
1411	—	?6	68	100	45	19	5	50
1412	—	87	83	58	11	27	58	44
1413	31	21	57[e]	60[f]	34	34	25	10
1414	41	58	86	101	54	57	22	66
1415	33	33	28	64	?3	31	4	25
Formula 3215E								
1201	—	—	—	—	—	—	—	—
1202	13	?3	—	—	—	—	—	—
1203	37	31	15	8	45	25	—	19
1204	—	—	5	5	—	5	5	10
1205	42	62	43	13	1	5	5	—
1206	—	22	54	62	6	3	3	10
1207	—	54	39	38	14	5	3	6
1208	51	31	10	?6	35	40	—	26
1209	—	—	10	3	32	—	7	3
1210	?6	4	39	?6	—	—	—	10
1211	19	21	5	33	5	4	—	5
1212	4	—	4	1	—	30	9	13
1213	25	49	22	60	—	5	12	7
1214	13	53	3	43	24	4	4	—
1215	77	83	61	37	68	54	90	80
1216	97	99	55	200	25	14	—	10
Females								
Formula 3215A								
975	—	19	5	?5[e]	—	5	5	—
976	—	61	36	46	41	31	40	26
977	—	35	22	6	20	20	17	12
978	4	3	26	34[e]	3	?4	8	16
979	17	5	5	5	5	10	5	9
980	31	61	30	15	16	14	—	—
981	9	40	5	—	—	—	—	—
982	—	—	5	10	36	—	—	5
983	—	—	—	—	—	—	—	—
984	21	16	7	77	22	30	19	5
985	?6	50	60	58	43	54	42	46
986	31	—						
987	12	78	20	?5	40	10	—	22
988	—	86[e]	21	?2	21	11	11	4
989	13	40	56	31	48	20	15	24
990	20	16	9	24	13	13	7	1
Formula ?9B								
135	133	47	23	56	—	—	—	—
139	—	—	12	—	13	—	—	—
143	6	?5	23	14	18	17	—	—
144		—	—	—	—	—	—	—
147	5	9	36	60	31	17	9	—
148	6	126	77	134[c]	47	46	33	14
151	46	16	33[f]	47	29	5	23	10
152	[illegible]	69	14	37	6	8	8	19
Formula 5018C								
1325		—	—	—	10			
1326		—	—	—	—	—	—	—
1327		4	14	10	7	3	5	11
1328	1	10	16	10	—	21	21	10
1330		11	24	32	—	10	—	5

Appendix IV (*continued*)

Subject number	Oatmeal with bananas and applesauce 28–41	42–55	56–83	84–111	Pears 56–83	84–111	Applesauce 84–111	Bananas 84–111
1332	—	15	33	21	6	36	14	46
1333	11	32	52	65	21	15	17	12
1334	21	10	19	—	10	—	—	—
1335	11	5	21	—	6	—	19	13
1336	10	30	—	6	6	—	—	6
1337	10	42	48	21	6	16	—	5
1338	10	79	20	26	16	—	—	6
1339	58	30	104	23	26	11	—	23
Formula Similac								
1375	14	11	3	3	4	6	—	13
1376	—	—	—	14	—	—	—	17
1377	18	—	7	4	13	12	8	9
1378	—	10	11	43	7	28	4	7
1379	52	53	43	73	35	87	27	20
1380	53	156	32	90	5	14	25	37
1381	20	35	38	18	11	17	—	—
1382	33	41	40	45	—	19	12	25
1383	18	56	25	3	14	4	4	9
1384	46	76	89	96	37	68	12	22
1385	—	5	11	21	2	18	—	13
1386	—	—	—	—	—	—	—	—
1387	—	5	31	22	23	20	5	11
1388	28	58	39	66	33	90	70	24
1389	72	73	28	39	8	8	17	31
Formula Formil								
451	—	—	27	38	24	14	10	4
452	—	19	—	—	—	—	—	—
453	—	—	—	—	—	—	—	—
454	19	10	18	32	4	24	14	17
455	5	6	19	37	23	14	29	14
456	—	—	—	—	—	—	—	—
457	10	21	48	96	58	88	41	23
458	29	112	112	41	46	25	4	5
459	4	3	10	17	12	14	7	—
460	12	61	68	50	39	32	32	5
461	39	19	67	76	42	10	29	48
462	8	—	9	—	—	—	—	—
463	36	10	43	33	38	34	—	—
464	19	20	4	19	9	10	—	—
465	26	44	31	18	17	8	—	12
466	58	58	43	29	29	20	9	4
468	—	—	—	—	—	—	—	—
469	13	10	2	4	2	—	—	—
Formula Modilac								
1421	22	13	29	45	21	23	13	11
1422	20	25	19	—	13	18	—	—
1423	20	11	39	17	20	6	—	6
1424	27	31	34	60	33	69	—	4
1425	8	53	48	—	52	—	—	—
1426	—	—	19	3	19	31	—	31
1427	14	43	26	—	11	—	6	—
1428	20	32	36	15	12	6	11	5
1429	19	13	7	19	6	3	10	23
1430	—	8	—	62	—	34	4	7
1431	10	—	—	23	—	—	9	2
1432	10	—	11	16	—	11	—	—
1433	33	118	91	80	66	70	32	17
1434	36	55	156*	114	30	15	37	86
1435	66	42	61	49	49	28	16	17

Appendix V. Average daily weight (g) of strained foods consumed by individual infants

Foods not included in study protocol

Subject	Age interval (days)	Food designation[a]	Quantity (g/day)
Males			
951	56–83	Dutch apple dessert	4
954	28–41	Orange juice	4
	84–111	Bananas with pineapple	2
177	84–111	Beets	3
130	56–83	Bananas	19
	84–111	Beets	4
	84–111	Sweet potatoes	4
140	56–83	Bananas with pineapple	4
	84–111	Bananas with pineapple	10
	84–111	Beets	4
153	42–55	Pears	46
	84–111	Beets	43
1361	56–83	Applesauce	9
	56–83	Bananas	10
1401	42–55	Pears	28
1403	42–55	Pears	22
1408	56–83	Applesauce	16
1409	28–41	Pears	10
1415	4 55	Pears	34
1216	4 55	Pears	40
Females			
975	84–111	Bananas with pineapple	5
	84–111	Peaches	5
981	4 55	Bananas	11
984	14–27	Pears	15
987	42–55	Pears	4
	56–83	Applesauce	3
	84–111	Applesauce with apricots	4
1337	56–83	Bananas	12
1339	56–83	Bananas	6
	56–83	Applesauce	18
452	4 55	Pears	9
1424	42–55	Vegetables, egg noodles and chicken	4
1426	56–83	Applesauce	15

[a] With one exception, these foods were strained food produced by Gerber Products Company. Subject 1424 received vegetables, egg noodles and chicken produced by H. J. Heinz Company.

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

161. Palmer, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966
167. Ivarsson, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 32.— 1966
168. Tuuteri, W. Fetal Scalp Discharges in Children, a Longitudinal Study. Sw. kr. 25.— 1966
169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bolman, Margot, Studies on Enuresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 22.— 1966
172. *Festschrift in Memory of Constantin Charvet.* Sw. kr. 33.— 1967
173. Walsh, S. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersen, Per Ove, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hirvonen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 23.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus infection. Sw. kr. 30.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress, Bergen, 1967.* Sw. kr. 33.— 1967
178. Biörck, Irène, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 23.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to E. Coli O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Günter, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 25.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 23.— 1968

Alex F. and Sprecher, Howard, A Review of Human Metabolism and Transport. Sw. kr. 25.— 1968

The intrapulmonary arterial pattern in normal in transposition of the great arteries. Sw. kr. 25.—

Andersen, Elm, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 45.— 1968

186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 23.— 1968
187. Karlberg, Petter, et al., The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1968
188. Meeuwisse, Gunnar W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 28.— 1969
190. Eklund, P. Tore, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 28.— 1968
191. Koivikko, Antti, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kouvalainen, Antti, Studies on the Serum Binding of Vitamin B₁₂ in the Newborn Human Infant. Sw. kr. 32.— 1969
195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 33.— 1969
196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 28.— 1969
197. Bendz, Rine, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 30.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Sanjur, Diva M., Cravioto, Joaquin, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 33.— 1970
201. Sutherland, Lynette E., Harnett, Phyllis, Rabe, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr, L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Annerén, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 33.— 1970
204. Berg, Kristian, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 33.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Eleventh Scandinavian Paediatric Congress.* Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 33.— 1970
208. Eeg-Olofsson, Orvar, *The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years.* Sw. kr. 21.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 33.— 1970
210. Rosberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. Sw. kr. 23.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Hakulinen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 33.— 1971
213. Lindhaus, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971
214. Samuelson, Göte, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 23.— 1971
215. Bergsman, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped children. Sw. kr. 23.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium.* Stockholm, August 30–September 1, 1970. Edited by Claes Thorén. Sw. kr. 33.— 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 33.— 1971
219. Jaffé, Doris, Hartroft, Stanley, Manning, Mary and Eleta, Graciela, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. Sw. kr. 23.— 1971
220. Hallman, Niilo, Bäckström, Leena, Kantero, Riitta-Liisa and Tiisala, Riitta, Studies on Growth of Finnish Children from Birth to Ten Years. Sw. kr. 30.— 1971
221. Bohman, Michael, A Comparative Study of Adopted Children, Foster Children and Children in Their Biological Environment Born after Undesired Pregnancies. Sw. kr. 23.— 1971
222. Johansson, Ekild, Plasma Magnesium Levels during the First Five Days of Life. Sw. kr. 30.— 1971
223. Fomon, Samuel J., Thomas, Lora N., Filer, Jr., L. J., Ziegler, Ekhard E., and Leonard, Michael T. Food Consumption and Growth of Normal Infants Fed Milk-based Formulas. Sw. kr. 33.— 1971

Price Swed. kr 25 —

Printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

7136

ACTA PÆDIATRICA SCANDINAVICA

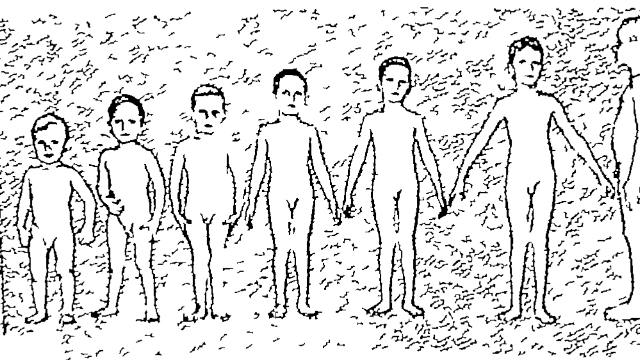
SUPPLEMENT 22[illegible]

A PROSPECTIVE LONGITUDINAL STUDY OF CHILDREN

DATA ON PSYCHIC HEALTH AND DEVELOPMENT UP TO 8 YEARS OF AGE

BY GUNNAR KLACKENBERG

ALMQVIST & WIKSELL



From the Pediatric Department of Karolinska Institutet at Karolinska sjukhuset, Stockholm, Sweden. (Head: J. Lind)
and the Pediatric Department of the University of Göteborg at the Childrens Hospital, Göteborg, Sweden. (Head: P. Karlberg)

A PROSPECTIVE LONGITUDINAL STUDY OF CHILDREN

Data on psychic health and development up to 8 years of age

by

Gunnar Klackenberg

To parents and children in
the study

ACKNOWLEDGEMENTS

This prospective study of children would never have materialized without the interest in the child as a whole which my clinical teacher Professor emeritus Arvid Wallgren has displayed. He has been extremely patient his endurance has been stimulating and his confidence a strength for me I am most grateful

Similarly I am indebted to Professor John Lind for the many ways in which he has supported and enthusiastically encouraged the work as well as for providing facilities for the study in his capacity as head of the Department of Pediatrics at Karolinska Sjukhuset

The many years required for a longitudinal study of growth carried out under uncertain financial conditions form a good test of the durability of the team that started the project I am therefore very pleased to note that the five people who began this work sixteen years ago are still on the job My deep thanks are chiefly due to the four original colleagues who have invested a great deal of emotional capital in the study With his clearsightedness helpfulness and eye for essentials Professor Petter Karlberg has been a source of inspiration all along for the study as well as for me personally Our psychologist Ingrid Klackenberg-Larsson and our pediatrician Henrik Lichtenstein have for many years undertaken the continual task of collecting psychic and somatic data in a matter-of-fact perceptive and knowledgeable manner It has been a pleasant experience to survey all the exact and concrete observations which have been noted in case records and computer cards and which form a foundation for this thesis I have further reason to thank my sister Ingrid Klackenberg-Larsson for the valuable criticism and discussions that have arisen out of her scrutiny of the manuscript

Our nurse Inga Svennberg has been most tactful and friendly in her handling of contacts with children and relatives Her ability to keep things running has been valuable for the study and for me

During some of the years when data were being collected for this work other persons with a psychological training also made valu-

able contributions It is a pleasure for me to mention the assistance provided by fil lic Jan Stensson over a series of years

Professor Ingvar Johannesson and Ass Professor Inga Engström have placed their knowledge at the disposal of the study for several years and I should like to thank them for the conversations and exchanges of opinion which have enriched my work.

In technical matters all secretarial assistance and the drawing of diagrams I have received invaluable help from Mrs Elvor Müller Her capacity obligingness and calm have been real assets and source of pleasure

I wish to thank Mr Patrick Hort for our exceedingly agreeable collaboration in translating the manuscript from Swedish.

During the last few years the processing of data has been undertaken in a most considerate manner by Mr Thorvald Landström at Göteborgs Universitet I am grateful for his help

The study has financially been supported by grants from

Centre International de l'Enfance
Swedish Medical Research Council
The Bank of Sweden Tercentenary Fund
Stockholms stadskollegiums Bidrag till vetenskapligt forskningsarbete
Carl-Bertel Nathhorsts Vetenskapliga och Allmännyttiga stiftelser
Första Majblommans Riksförbund
Syskonen Wesséns Stiftelse
Findus AB

CONTENTS

		Page
	Introduction	6
Chapter I	List of the papers comprising this thesis	8
Chapter II	The study organized as teamwork - the team	10
Chapter III	Summaries of previously published paper 1 and 2 in Acta paed. scand 1968 suppl 187 1 Introduction, design and aims of the study 2. The social background and its changes during childrens first three years of life	11
Chapter IV	General description of methods	13
Chapter V	Changes in the composition of the sample up to 8 years Losses from the sample	16
Chapter VI	Advantages and disadvantages of different ways of data-gathering	
	Aspects of longitudinal versus cross-sectional studies	19
	Aspects of the use of prospective versus retrospective data in everyday and scientific work	21
	Validity and reliability of reported observations	22
Chapter VII	Statistical analysis	26
Chapter VIII	Summaries of the remaining previously published papers 3 Breastfeeding and weaning: some social psychological aspects 4. The sleep behaviour of children up to three years of age 5 Some differences in infant feeding and elimination training in five European longitudinal samples 6 Differences in age f walking in five European longitudinal samples	28
Chapter IX	Non-nutritional sucking in ages from infancy up to 6 years of age	
	Introduction	32
	Frequency	34
	Sex differences	
	Etiological view points	
	Prolonged fingersucking in relation to emotional factors	

		Page
	Sequelae of fingersucking: malocclusion	48
	articulation troubles	50
	Parental reactions	52
	General discussion	54
	Summary	57
Chapter X	Nailbiting	
	Introduction	61
	Frequency	61
	Sex difference	62
	Persistence	62
	Covariation with other variables	65
	Parental reactions to nailbiting at 2-5 years	70
	Summary	70
Chapter XI	Rhythmic movements in infancy and early childhood. Headbanging headturning and rocking	
	Introduction	74
	Frequency	75
	Persistence	77
	Covariation-testing	78
	Effects of longlasting jactatio	81
	Summary	82
Chapter XII	Expectations and reality concerning toilet training	
	Introduction	85
	Commencement of training	86
	The development of functional control of the bladder	90
	When is control attained over the bowels?	92
	Data-summary in tabular form	94
	The relation between the duration of training and the functional control	95
	Reactions to toilet training	99
	Coercion and training results	105
	The relation of coercive training to other variables	107
	Regular bowel functioning and its relation to training	110
	Bed wetting day wetting, encopresis	112

		Page
	Covariation in different forms of instability	119
	Countermeasures against night wetting during the toilet training period	122
	Instability and intelligence	123
	Summary	125
Chapter XIII	A prospective longitudinal view of early speech impediments in a normal child sample	128
	General introduction	129
	I Impediments in the flow of the speech	130
	Frequency	130
	Persistence	132
	The onset of stuttering in relation to accident or fright	134
	Non-fluency in speech in relation to speech maturity	138
	Co-variation of stuttering and other variables	141
	II Enunciation defects Introduction	147
	Frequency Sex difference	150
	Follow up of speech retardation	152
	The covariation of speech retardation and behavioural variables	153
	Enunciation defects speech maturity and ability	156
	Summary	158
Chapter XIV	Further studies on sleep behaviour in a longitudinally followed up sample (principal ages for this section 4-8 years)	161
	Introduction	161
	Sleeping habits and duration of sleep	162
	Sleeping place	165
	Resistance at bedtime	169
	Night waking	171
	Frequency Persistence	172
	Night waking behaviour	174
	Covariation of night waking with certain environmental variables	175
	Parental response to night waking	178
	Somnambulism	179
	Bad dreaming	181

		Page
	Covariation of somnambulism and bad dreams	182
	Summary	184
Chapter XV	Temper tantrums and destructiveness	
	Introduction	187
	Frequency of temper tantrum	188
	of destructiveness	189
	Persistence of temper tantrum	190
	of destructiveness	191
	Covariation temper - destructiveness	191
	Summary	193
Chapter XVI	Tics in statu nascendi	
	Introduction	195
	The frequency persistence and nature of tics	197
	The relevance of emotional factors	202
	Covariation with other variables	205
	Summary	208
Chapter XVII	Symptom changes and symptom load	
	Introduction	211
	Symptom changes: results	212
	Symptom load	218
	Summary and conclusions	222
Chapter XVIII	General summary	225

INTRODUCTION

For many years now longitudinal prospective studies of growth co-ordinated by Centre international de l enfance (C I E.) have been conducted in London Paris Brussels Zürich and Stockholm (Solna) whereby development behavioural and somatic growth data are recorded for child samples at various stages on uniform lines and using the same methods Continual comparable data for the first years of life have also been obtained from children in two African centres (Kampala and Dakar)

Before venturing on extensive international comparisons on the requisite scale of the growth norms of upbringing and development characteristics of children from different cultural environments it has been essential for the various national centres to analyse the host of information collected over the years in various quarters. The present study is mainly to be regarded as part of this effort to begin by penetrating our own results

This report on the longitudinal Stockholm study comprises an analysis of part of the psychosomatic data collected during the first eight years of the children s lives The object is to examine the development of certain habits incorporated in the child s adjustment as it grows up Comprehensive structured interviews with mothers assessments of the child and a variety of tests administered at regular intervals are used to illustrate the stability of skills developed, together with the considerable variations between individuals of the same age Pride of place is given in this study to the mutual relationships between different behavioural variables and between those variables and various kinds of environment The development of the behavioural characteristics chosen for analysis is described against the background of a large variety of social factors The child s somatic state of health has also been included as a background factor where applicable

The present report forms part of a series of published or scheduled essays on child development The aims and general structure of the project have already been presented in Acta paed. scand. 1966

suppl 187 The same issue also included a number of essays containing social somatic and psychic data from the first three years of the children s lives The eight papers presented here should be viewed in conjunction with six published previously (four in the abovementioned Acta paed. supplement one in Journal child psychol and psychiat 1965 one in Human Biology 1966)

CHAPTER I

LIST OF THE PAPERS COMPRISING THIS THESIS

1 The development of children in a Swedish urban community A prospective longitudinal study Introduction, design and aims of the study Description of the sample
Karlberg P Klackenberg G Klackenberg-Larsson I, Lichtenstein H. Stensson J and Svennberg I (Summary page 12)

2. The social and family background and its changes during the childrens first three years of life
Klackenberg G Karlberg P Klackenberg-Larsson I. Lichtenstein H. Stensson, J and Svennberg I. (Summary page 13)

3 Breast-feeding and weaning: Some social psychological aspects
Klackenberg G and Klackenberg-Larsson, I. (Summary page 29)

4. The sleep behaviour of children up to three years of age
Klackenberg G (Summary page 29)

5 Some differences in infant feeding and elimination training in five European longitudinal samples
J child psychol and psychiat 6: 179-201 1965
Hindley C Filliozat A.M. Klackenberg G Nicolet-Meister D Sand E.A. (Summary page 30)

6 Differences in age of walking in five European longitudinal samples Human Biology 38: 4: 364-379 1966
Hindley C. Filliozat A.M. Klackenberg G Nicolet-Meister D Sand, E.A. (Summary page 31)

7 Non-nutritional sucking in ages from infancy up to 8 years of age
Klackenberg G

8. Nailbiting
Klackenberg, G

9 Rhythmic movements in infancy and early childhood.
Head-banging head-turning and rocking
Klackenberg G

10 Expectations and reality concerning toilet-training
Klackenberg G

11. A prospective longitudinal view of early speech impediments in a normal child sample
Klackenberg G

12. Further studies of sleep behaviour (principal ages 4 - 8 years)
Klackenberg G

13 Temper tantrum and destructiveness
Klackenberg, G

14 Tics in statu nascendi
Klackenberg G

15 Symptom changes and symptom load.
Klackenberg G

CHAPTER II

T H E   S T U D Y   O R G A N I Z E D   A S   T E A M W O R K - T H E   T E A M

The Swedish study initiated by Arvid Wallgren was planned in the autumn of 1954 when Petter Karlberg now Professor Karlberg and I attended the first Annual Growth Meeting of the C I E. in Paris During the winter we were joined by a psychologist L. Klackenberg-Larsson, and a pediatrician Dr Henrik Lichtenstein, and set about planning the Clinic for the Study of Children s Development and Health which was established in January 1955 at the Department of Pediatrics at Karolinska Sjukhuset A nurse I. Svennberg joined the team at that time.

These five persons have been engaged in the work from the start and are still participating.

As the volume of work increased with the inclusion of additional children over a three-year period it became necessary to obtain further assistance with the collection of all the data. Consequently the following persons have been associated with the study at times in the period covered by the present thesis

B. Olofgöre psychologist	1/3 1958 - 28/2 1959
K. Widström,	1/3 1959 - 31/3 1960
J Stensson,	1/4 1960 - 1/9 1962
B. Kellbom	1/4 1963 - 31/3 1964

In 1963 Ingvar Johannesson, now Professor Johannesson, joined the team and with his colleagues is following up the children in the school situation.

Since 1965 Assistant Professor Inga Engström has been helping with the future design of the study

SUMMARIES OF PREVIOUSLY PUBLISHED PAPER 1 AND 2 IN ACTA PAED. SCAND 1968 SUPPL. 187

Paper 1. Introduction, design and aims of the study. Description of the sample.

The Stockholm study the first prospective longitudinal study of child development and health in Sweden is presented and its objectives and intended design discussed. Of the sample of 212 children 14 % were recruited from an obstetrical clinic and 86 % by an invitation to every fourth pregnant woman at the Solna maternity welfare centre to participate in the study In the event of anybody invited to participate being prevented from doing so the invitation was passed on to the fourth next mother Only 3 % of those originally approached considered themselves unable to participate

The two recruitment procedures resulted in two samples of different sizes which were later amalgamated after analysis and comparisons to form the basis of the study Socio-economically the total group represents a truer picture of the community from which it has been drawn than does the maternity welfare centre group alone Insofar as comparisons have been possible with known conditions in the recruitment area, which is part of Greater Stockholm the sample has in most respects agreed well not only in terms of social class distribution but also in terms of the age distribution of the mothers the proportion of children born out of wedlock, the proportion of children conceived out of wedlock and the distribution of children by order of sequence gestation period and weight at birth.

The number of boys (122) which in spite of the antenatal recruitment was unexpectedly large in relation to the number of girls (90) was not statistically unacceptable from the point of view of sampling A t-test showed that the probability of such a random distribution exceeded 5 %.

In view of the recruiting methods employed together with the established similarities between the sample and known conditions in the

Stockholm area we have found it probable and have assumed by way of a working hypothesis that the sample represents not only itself but also a wider area, a Swedish city community

Paper 2. The social background and its changes during the children s first three years of life

The composition and social background of the families participating in the study are analysed with regard to a number of important variables: housing conditions education occupation income size of family age of parents and marital status The families are distributed throughout the social scale in a manner representative of Stockholm.

A new international system of social classification devised by Graffar was employed parallel to the Swedish occupational system. According to Graffar s system which takes into account housing conditions education occupation and income on five-point scales a family is socially characterized by a social score of between 4 and 20 All the variables in the grouping system except education are on the whole normally distributed. The mothers gainful employment its incidence and stability are given particular attention as an important background factor during the children s first years of life

The average social standard of the families improves during the children s first three years of life Overcrowding which is considerable when mother and child return home from the maternity hospital declines appreciably during the first years The families incomes have improved. In all probability the changes for the better which can be discerned through Graffar s system of points reflect the general rise in social standards in Sweden during these years especially as regards the social stabilization undergone by the youngest families.

CHAPTER III

SUMMARIES OF PREVIOUSLY PUBLISHED PAPER 1 AND 2 IN ACTA PAED SCAND 1968 SUPPL. 187

Paper 1. Introduction, design and aims of the study. Description of the sample.

The Stockholm study the first prospective longitudinal study of child development and health in Sweden, is presented and its objectives and intended design discussed. Of the sample of 212 children 14 % were recruited from an obstetrical clinic and 86 % by an invitation to every fourth pregnant woman at the Solna maternity welfare centre to participate in the study In the event of anybody invited to participate being prevented from doing so the invitation was passed on to the fourth next mother Only 3 % of those originally approached considered themselves unable to participate

The two recruitment procedures resulted in two samples of different sizes which were later amalgamated after analysis and comparisons to form the basis of the study Socio-economically the total group represents a truer picture of the community from which it has been drawn than does the maternity welfare centre group alone Insofar as comparisons have been possible with known conditions in the recruitment area which is part of Greater Stockholm the sample has in most respects agreed well not only in terms of social class distribution but also in terms of the age distribution of the mothers the proportion of children born out of wedlock the proportion of children conceived out of wedlock and the distribution of children by order of sequence gestation period and weight at birth.

The number of boys (122) which in spite of the antenatal recruitment was unexpectedly large in relation to the number of girls (90) was not statistically unacceptable from the point of view of sampling. A t-test showed that the probability of such a random distribution exceeded 5 %.

In view of the recruiting methods employed, together with the estab-

Kind of information and examinations done	Age at investigation: ante-natal	lying in	1	3	6	9	12	18	2	3	4	5	6	7	8
			months						years						
__Ratings__															
Child by psychologist			x	x	x	x	x	x	x	x	x	x	x	x	x
Mother											x				
__Attitude-scale__															
Schaeffer and Bell															
for mother											x				
father											x				
__SOMA__															
__Structural interview concerning health and alimentation__ form II			x	x	x	x	x	x	x	x	x	x	x	x	x
__Clinical examinations__ form II			x	x	x	x	x	x	x	x	x	x	x	x	x
Somatic measurement form III			x	x	x	x	x	x	x	x	x	x	x	x	x
Hand, knee X-ray			x	x	x	x	x	x	x	x	x	x	x	x	x
__SOCIAL CONDITIONS__ form 0							x		x	x	x	x	x	x	x
social chart 1-3 yrs (longitudinal)										x _					

The data on which the results presented here are principally based are taken from the structured interviews Brunet-Lezine and Terman-Merrill development and intelligence tests have been used to elucidate the relationships to different behavioural variables The relations to the various personality tests will be dealt with in later reports. Evaluation of these tests is not yet complete The child psychologist s assessment of the child in different variables on a five-point rating scale has been utilised for certain development characteristics Similarly the clinical findings of the pediatrician have served as a background. The various data in the comprehensive social questionnaire have been used to illustrate the argument throughout

Each of the three interview forms (four at 4 - 5 years) concerning the child s behaviour in general and in special circumstances (e g separation from the home accidents illness etc) contains 60 items These forms are designated V VI VII and IX (the last not used here) The alternative answers are rarely confined to a categorical "yes or no Usually the mother being interviewed has been offered a range of alternative answers enabling her to make graded or qualified statements concerning the child s symptoms together with their frequency and duration Appendix 1 contains the items used as material and forming the basis of the essays in this report The complete questionnaires forming the basis of the international part of the investigation are given in A base-line of investigations for longitudinal growth studies of the child (Falkner 1955)

Owing to the financial considerations dictated by the time-consuming investigations data were collected at the age of 6 years and above partly with the aid of a questionnaire sent to the mothers homes When the child and its guardian visited the clinic for examination the questionnaire was completed by the psychologist In addition to this supplementary check a brief structured interview was held on certain selected items This difference of procedure in the collection of data at ages before and after six years has in a way impaired the continuity of the investigation One can only speculate as to the extent to which it has also affected the result Many items are of such a kind that the deviant symptomatic manifestations have the same chance of being noted regardless of the circumstances while others are liable to be given another emphasis by the mother when she is alone than when she is guided by questions from the trained specialist For further details the reader is referred to the selection of questions used at 6 - 8 years given in Appendix 1

CHAPTER V

CHANGES IN THE COMPOSITION OF THE SAMPLE UP TO 8 YEARS LOSSES FROM THE SAMPLE.

There are great difficulties and risks involved in a longitudinal study extending up to the age of 18. Apart from the financial hazards there is the risk of invested capital failing to give a sufficient return owing to drop-outs from the sample The objective of recruitment is to obtain a sufficiently large representative sample to facilitate reasonably reliable statistical computations Once this has been achieved, it is necessary to maintain the subjects motivation to participate If a family moves away from the site of the investigation their continued participation will probably stand or fall by the distance they now have to travel from home Continued participation is accepted even if a child moves to a different geographical environment from its original metropolitan surroundings which has occurred in a few cases The present investigation has been favoured by the relatively generous employment opportunities of the metropolitan area coupled with the congested nature of the housing market It is much easier to keep the families interested if contacts and investigations at the clinic are always handled by the same staff These conditions have fortunately been satisfied in the Stockholm study thus making it possible to preserve the continuity of assessments to a very great extent

A certain drop-out is inevitable No continual long-term investigations of this kind, representatively recruited from different levels of society have yet been published without reporting a heavy drop-out (1) If the people who drop out do so because they move far away from the place where the investigation is being conducted, this can be regarded as a random circumstance although socially speaking it can lead to a skew distribution of the sample A more severe loss is sustained from the point of view of evaluation of the results obtained and the probable general validity of those results when a family stops partiaipating for lack of interest This may conceal difficulties which have arisen in balancing the domestic emotional situation. The people concerned do not want to have their children exposed unnecessarily by detailed studies nor do they themselves want to be provoked by interviews Motivations to this effect are seldom ex-

pressed so explicitly as this would suggest In various connections however one can discern something of the true reason for discontinuation. This reduces the available basis for symptom frequencies and etiological symptom studies. An attempt is made below to elucidate the causes of the - fortunately - small losses occurring in this study

At the conclusion of the random recruitment the sample amounted to 212 cases During the period up to and including 8 years covered by this report 12 children, i e 5 6 % of the original number had definitely ceased to participate in the study Of these 7 are girls and 5 boys with the result that the numerical superiority of the boys has become even more pronounced than it was at the beginning of the study

The final investigations of those who have dropped out of the study occurred at the following ages and for the following reasons

Last investigation at	No	Cause Removal	Death	Psychic reasons lack of interest
12 mths	2	2		
18	1	1		
36	4	1		3
48	2			2
60	1	1		
72	2	1	1	

Thus half of the twelve have moved to remote areas of Sweden or abroad. One boy was killed in a road accident at the age of 6 This leaves 5 children (3 ♂+ 2 ♀) who for various reasons have not been willing to continue after the age of 3 - 4 One mother (belonging to Jehovah s Witnesses) gave reasons of religious principle Another declined to give any reason; there was nothing exceptional about the development or behaviour of her child. In the three remaining cases the inconvenience entailed by the extensive investigation was said to be so great that the parents wished to withdraw Two of these children were so noisy and restless when they were being examined

that the mothers found this among other things a strain. Despite intensive efforts to induce the mothers to change their mind, contact had to be discontinued. Finally one boy suffered from synostosis cranii with obvious mental retardation. Since he was frequently in hospital the mother considered these investigations sufficient There seemed little point in retaining the boy in a so-called normal child sample since the deviation was clearly pathological

This slight drop-out affected all social groups Changes in the percentage distribution according to the Graffar five-point scale are not more than 1 % in either direction. Far greater than these changes in registered social group status is the rise in social standards undergone by the group during these 8 years which reflects percentage differences of up to 20 %.

Only one of the 12 children ceasing to take part in the study was born out of wedlock. Thus the drop-out from the 23 children born out of wedlock who were originally recruited was proportionally the same as for the sample as a whole The educational level of the group of mothers who have ceased to take part in the study corresponds very closely to that which is representative of the original sample

Conclusion. The drop-out from the sample during the first eight years of the children s lives has only to a minor extent been due to lack of interest on the part of the mothers Nor has it resulted in any notable changes in the social composition of the sample

REFERENCES

1 Stone A.A. and Onque G.O : Longitudinal studies of child personality Harvard University Press Cambridge Massachusetts 1959

CHAPTER VI

ADVANTAGES AND DISADVANTAGES OF DIFFERENT WAYS OF DATA-GATHERING

Aspects of longitudinal versus cross-sectional studies

Prospective or anterospective longitudinal studies with reference to child health and development are here taken to imply that the same individuals are continually observed in adequate studies or behavioural assessments at regular intervals during their childhood. The intervals between studies will vary according to the changes in development which are to be investigated and according to the ages of the children. The more rapidly a development trait a skill a characteristic or a bodily measurement changes the more frequently studies should be made to investigate the growth pattern. If a longitudinal follow-up is to be a practical proposition it must also take into account the visiting frequency for which parents and children can be motivated Another limitation is imposed by financial considerations A project which sets out to trace individual progress from birth to adulthood is bound to be expensive and the scientific return must be reasonable in proportion to the financial outlay

A great deal of the knowledge of child development has been derived from cross-sectional investigations of representative samples from different age groups Thus the data obtained on different occasions have not originated from the same children but from groups of different children at different ages A cross-sectional study takes far less time Results are obtained in proportion to the immediate work input and are not affected by the time which elapses before the individual child attains maturity It is invariably easier to obtain fully representative samples in cross-sectional investigations where drop-outs can be compensated by new recruitment In some respects however the cross-sectional investigation is inferior to the longitudinal follow-up When studying relations between previous observations and subsequent events with a view to constructing a model for prediction the only resort is continual observation of the phenomenon to be studied.

A child s mental and bodily development proceeds uninterruptedly but by no means in a straight line Periods of rapid development alternate with periods of steadier progress Children attain these periods at different ages Consequently a cross-sectional investigation of children of a certain age yields data from children at different stages of development with the result that there is generally a great deal of variation in any single age group Practically any behaviour can appear normal A bodily measurement or a behavioural characteristic can be accommodated within the normal deviations afforded by the cross-sectional investigation at the same time as the development of the individual child at the age in question may deviate from the optimum rate of development for which it is genetically programmed. The principal of the longitudinal follow-up which is gaining increasing practical currency in connection with preventive child care is that progress regression or deviant development at certain ages is assessed in relation to the initial situation together with achievements during earlier stages Knowledge or normal long-term development symptom variation and symptom persistence is essential for an adequate assessment of the value of current observations concerning the individual child.

Data concerning sleep are a case in point We know from cross-sectional figures that a fairly high percentage of children at different ages wake up night after night or at least sleep for only a few hours at a time But these figures do not tell us whether it is the same children who deviate in the various age groups in other words whether sleep disturbances or small sleep requirements are a characteristic developmental pattern in certain children or merely a temporary phenomenon. Thus longitudinal studies of a representative number of children provide a more reliable frame of reference for the decisions that have to be taken daily by pediatricians and child psychiatrists.

Aspects of the use of prospective versus retrospective data in everyday and scientific work

In locating the cause of a behaviour use is always made in clinical work of the anamnestic data which parents are able to provide The case history plays a major part in the diagnosis The therapeutic measures taken are related to these data as well as to what has been revealed by the investigations If records are not available from the child s earliest years the parent s memory observance and even their interpretations will be important for diagnosis and treatment Consequently clinics are often consigned to the use of available retrospective data This is a necessary resort which judiciously applied can produce satisfactory results

Retrospective data have also been frequently used in scientific investigations The mother s recollections are recast in the form of facts In these contexts reliability is of the utmost importance Investigations of the selective and incomplete manner in which memory functions have cast doubt on certain retrospective data which should accordingly be used with care

Pyles et al (3) found on comparing antero- and retrospective data from the longitudinal Berkely study that even when their children were no more than 21 months old, mothers could give a reliable statement of their weight at birth but had often forgotten important details concerning their own state of health during pregnancy as well as facts connected with their deliveries The same uncertainty surrounds conclusions on the psycho-motoric development of children based on recollections several years later (2) Chess et al (1) noted from their experience of the longitudinal New York investigation that as regards the development of behavioural problems significant distortions in development reporting had arisen in one third of the cases within the space of a few years They also point out the risk of certain parents attempting to force their recollections of behavioural development into generally accepted theories of cause and effect "The danger of such a self-fulfilling prophecy should lead to careful scrutiny of retrospective behavioural data when the nature of recall could be influenced by the knowledge of the theory" Robbins (4) alludes to similar hazards in the use of retrospective data concerning child handling methods

when he concludes: As a result there may be a self-perpetuating 'validation with experts opinion influencing parental reports which in turn influence the experts"

For the above reasons the prospective method of investigation must be superior to the retrospective But the prospective investigation is also based upon the memory of the observer although a far shorter memory is called for so that the facts obtained are more reliable In the present study the interval between the collection of facts varies from one to three months during the first year of life up to six months during the second year and up to 12 months subsequently More frequent investigations are again conducted during puberty with regard to certain data. Moreover much of the data on which investigations of behaviour are based are on-the-spot observations made in connection with the investigation itself

Validity and reliability of reported observations

One important question concerns the validity of the observations reported. It is of course the mother who is best acquainted with the child s behaviour Longitudinal investigations are practically impossible if the demands of science include that a trained outside observer be continually at the child s side Sources of error are reduced by the detailed psychological and somatic investigations recurring at regular intervals together with the mother s structured interview statements This is particularly true of reports concerning factual events (e g accidents periods in hospital or children s homes social data) or striking behaviour (e g motoric skills speech defects tics rhythmic movements bedwetting daytime wetting etc) The assessment of expressions of feelings involves a larger element of subjective evaluation, Since the norms concerning what is great and small are dependent on the experience mood and temperament of the observer Parents have no uniform scale of measurement for the temperature of an emotional climate nor have they any calibrated dimensions to indicate the degree of agressiveness or sensitivity As far as interviews are concerned, we are confined to the views expressed by a parent according to his or her individual frame of reference The interviews included to afford certain opportunities of measuring expressions of feelings in exampli-

fied behaviour per unit of time or more generally by expressions such as "usually" often sometimes seldom" or never" In this way the gradation represents a differentiation which brings out certain important differences Clearly a child that throws itself on the floor every day in rage or despair exhibits a symptom of its feelings more intensively than another child who reacts in the same way about once a month.

In all respects efforts have been made to obtain data which as far as possible are referable to factual descriptions rather than interpretations and evaluations A similar procedure has been validated in the longitudinal New York investigation by mutually independent outside psychologists carrying out a number of assessments of the child s behaviour and noting their observations for comparison with the mother s statements (5) The result of these comparisons was that each of the direct observations agreed with the parent interviews at a probability level of 01

One weakness revealed in the long-term comparison of certain kinds of behaviour is that the interview question may have been phrased somewhat differently at a later stage than during the first five years Even if the principal content is the same a different shade of meaning can result in a different gradation especially if the scale has been given another name This is illustrated by the question on night waking Up to 5 years the mother was asked: "Has he/she woken up during the night since last time? The alternative answers which the psychologist had to choose from were distributed on the scale: nightly several times nightly once 3 - 6/week, 1 - 2/week less never At 6 - 8 years the question read: "Has he woken up at all during the night? The alternative answers: always often sometimes seldom, never The six points of the scale reflecting different frequencies of sleep disturbance during the first five years of life are readily transformed into five (nightly several + nightly once = nightly) But the question is whether this corresponds to always in the alternative answers for the subsequent years Obviously if a child wakes up every night it satisfies the parent s criterion of always But this may also include a somewhat lower frequency than the nightly one The boundaries between always often and sometimes are less definite

than the attempts at gradation by unit of time which were used during the preceding years

There is little danger of missing trends towards changes in individual or group behaviour from one year to another A five-point or in exceptional cases three-point scale will in all probability reveal palpable differences by a scale discrepancy of two points or more even if the assessment is made at yearly intervals Thus *according to our assumption* each child *is characterized* by the position it occupies on the scale or by the position next to it In an investigation covering several years there is bound to be a risk of questions and answers acquiring a somewhat different emphasis from what was originally the case

The children in this longitudinally followed up sample were not treated at the *clinic* nor have their parents received any special guidance; like other parents they have had to consult the regular medical and child guidance facilities or a private doctor if they have felt this to be necessary For obvious ethical reasons the investigation team could not stand idly by if diseases were diagnosed *or serious deficiencies* revealed. In such cases the parents have been given help in establishing the contacts which have been thought necessary and which they themselves have wished for The primary task however has been the continual accumulation of data from sufficiently related points in the child s development In this way the children and parents have come to form a special group the object of friendly and very close interest It is hard to say how far this has resulted *in a different parental attitude towards the children* from what would normally have been the case Interviews may conceivably arouse second thoughts which in turn may develop into reflection and ripen into wisdom. In this way the unreflecting parent may become more aware of the problems involved. Few peopl are entirely unaffected by a detailed neutral interview concerning a child s behaviour It is impossible to say to what extent unintentional influences occur *in a longitudinal investigation* or what the nature of such influences would be In the interviews a deliberate attempt has been made to obtain data that refer as far as possible to observed behaviour and actual events.

REFERENCES

1 Chess S Thomas A. and Birch, H.: Distortions in developmental reporting made by parents of behaviorally disturbed children. J Amer Acad. Child Psychiatry 5:226 (1966)

2 Haggard, E.A. Brekstad, A. and Skard A.: On the reliability of the anamnestic interview J Abnorm. Soc Psychol 61:311-318 (1960)

3 Pyles M.K. Stolz H.R. and Macfarlane J : The accuracy of mothers reports on birth and developmental data. Child Develop. 6: 165-176 (1935)

4 Robbins L.C : The accuracy of parental recall of aspects of child development and of child rearing practices J Abnorm. Soc Psychol 66:261 (1963)

5 Thomas A. Chess S Birch H. Hertzig M. and Korn S : Behavioral Individuality in Early Childhood. New York University Press 1963

CHAPTER VII

STATISTICAL ANALYSIS

The information collected has been transferred to computer cards and then to the magnetic tape of the computer Since the investigation has been in progress for several years various types of computer have been used. Most of the results presented here have been obtained with programmes for the D 21 Saab Earlier analyses were carried out using an IBM 2.

The methods of statistical analysis employed are conventional and will be found in any up-to-date standard work on statistics. (1 3 4 5)

X^2 has been the method most frequently used. Observed frequencies of a defined observation have been related to the frequency which a random distribution has been theoretically assumed to produce In practically every case the entire material has been used for each analysis Sometimes as a tentative test only extreme groups have been used, but they have generally been supplemented by a division of the entire group into two or three (fourfold and sixfold tables respectively)

In the variable analyses containing quantitative numerical magnitudes mean values standard deviations and mean errors have been calculated. The differences between mean values have been tested in ordinary t-tests

Median value differences between two samples (e g boys and girls) have been tested for significance by X^2 comparison of frequencies of deviation from the median in the aggregate sample the "median test

Correlation estimates ad modum Pearson have been used to elucidate the degree of correlation. The probability of the estimated coefficient of correlation not being random has been tested using the methods specified.

Certain comparisons have been made with the simple sign -test and the confidence limits have been obtained directly from Scientific tables (2)

The three levels of significance used throughout are $p < 001$ (= highly significant) $p < 01$ (= significant) and $p < 05$ (= probably significant) Sometimes the value of the degree of significance between these three is indicated to show the proximity to the higher level of probability

REFERENCES

1 Croxton, F : Elementary statistics with applications in medicine and the biological sciences Dover Publications Inc New York 1953

2. Documenta Geigy Scientific Tables Seventh Edition, J R. Geigy S A. Basle Switzerland, 1970

3 Mc Nemar Q.: Psychological statistics John Wiley and sons Inc New York and London 1962

4. Snedecor G W : Statistical methods The Iowa State University Press Ames Iowa 1964

5 Siegel S : Nonparametric Statistics Mc Graw-Hill New York 1956

CHAPTER VIII

SUMMARIES OF THE REMAINING PREVIOUSLY PUBLISHED PAPERS

Breast feeding and weaning: some social psychological aspects

Differences with a statistical significance on at least the 2 % level were observed as follows:

1 boys were weaned later than girls
2. older mothers (26 years and over) continued breast feeding longer than younger mothers (< 26 years)
3 mothers in higher social classes continued breast feeding longer than mothers in lower social classes (Graffar I + II vs III vs IV + V)
4 better-educated mothers continued breast feeding longer on average than mothers with only compulsory elementary education
5 mothers who continued breast feeding for more than 6 months were on average possessed of greater self-confidence method and calm.

Weaning before six months was very seldom occasioned by the mother s resumption of gainful employment The commonest reason was that the supply of mother s milk failed without any demonstrable influence from external factors During the first months the mothers attitude to breast feeding while this was in progress was generally positive but this professedly positive attitude was of no predictive value regarding the duration of breast feeding

The sleep behaviour of children up to three years of age

Mean values and standard deviations are given for length of sleep at 6 9 12 18 24 and 36 months. There is no appreciable correlation between the total length of sleep per day and season or hours of sunshine. The correlation coefficient in a comparison of length of sleep at different ages was at most .49 No statistical relation could be established between length of sleep and a large number of tested variables including overcrowding and gainfully employed mothers

Different forms of wakefulness which occurred were analysed. These included resistance to bedtime preparation evening wakefulness and night waking Sleep disturbances were a recurrent characteristic of children s sleep behavior during annual periods For none of the periods did the occurrence of nightly waking fall below 23 % No connection could be established between night waking an environmental factors On the other hand the firstborn children showed a significant frequency of resistance to bedtime preparations Similarly the experience of separation from the family owing to a period in hospital or childrens home or some other form of care in strange surroundings led to resistence to sleep by children aged between 2 and 3

The group of children who had been consistently bad sleepers for at least 2 years was compared with children who had slept without disturbances Of the variables tested only overcrowding and late weaning were related to this tendency to wakefulness Of all the methods employed for settling children in case of night waking the mothers claimed that the most effective under 18 months was to give them food while for children over 18 months the best solution was to let them get into the parents beds

Differences in infant feeding and elimination training in five European longitudinal samples (Hindley et al)

The ages for weaning from breast and bottle feeding and for the start of toilet training were compared in child samples from Brussels London Paris Stockholm and Zurich. Large discrepancies were found in all three respects

The median age when the last breast meal was discontinued varied from 0 9 months in the Brussles sample to 4 5 months in the Stockholm sample

The median age at wich bottle feeding ceased ranged from 13 3 months in the Zurich sample to 17 5 months in the London sample

In the case of the age at which continuous toilet training was started, the variation was from a median of 4 6 months in the London sample to 12 4 months in the Stockholm sample

The differences between the samples were considerably greater than those within each sample that were attributable to differences in social score

The differences in cultural patterns and in attitudes to methods of handling children were discussed.

Differences in age of walking in five European longitudinal samples (Hindley et al)

The study was designed to compare data on the ability to walk without support for children from the five longitudinal studies in which information had been collected concurrently and with the same technique The number of children in the individual samples ranged between 152 and 272. In all the samples the cumulative distribution of the age of first walking described a practically straight line between the 5th and the 95th percentile on a logarithmic scale indicating normality

The age of first walking did not differ by social group or by sex in any of the samples Significant differences were found, on the other hand, between the median ages for each of the five samples Conceivable causes of this were discussed, e g genetic factors feeding conditions and the way the parents cared for the child.

Different forms of wakefulness which occurred were analysed. These included resistance to bedtime preparation evening wakefulness and night waking Sleep disturbances were a recurrent characteristic of children s sleep behavior during annual periods For none of the periods did the occurrence of nightly waking fall below 23 % No connection could be established between night waking an environmental factors On the other hand the firstborn children showed a significant frequency of resistance to bedtime preparations Similarly the experience of separation from the family owing to a period in hospital or children s home or some other form of care in strange surroundings led to resistance to sleep by children aged between 2 and 3

The group of children who had been consistently bad sleepers for at least 2 years was compared with children who had slept without disturbances Of the variables tested, only overcrowding and late weaning were related to this tendency to wakefulness Of all the methods employed for settling children in case of night waking the mothers claimed that the most effective under 18 months was to give them food while for children over 18 months the best solution was to let them get into the parents beds

Differences in infant feeding and elimination training in five European longitudinal samples (Hindley et al)

The ages for weaning from breast and bottle feeding and for the start of toilet training were compared in child samples from Brusseles London Paris Stockholm and Zurich. Large discrepancies were found in all three respects

The median age when the last breast meal was discontinued varied from 0 9 months in the Brussles sample to 4 5 months in the Stockholm sample

The median age at wich bottle feeding ceased ranged from 13 3 months in the Zurich sample to 17 5 months in the London sample

In the case of the age at which continuous toilet training was started, the variation was from a median of 4 6 months in the London sample to 12 4 months in the Stockholm sample

The differences between the samples were considerably greater than those within each sample that were attributable to differences in social score

The differences in cultural patterns and in attitudes to methods of handling children were discussed.

Differences in age of walking in five European longitudinal samples (Hindley et al)

The study was designed to compare data on the ability to walk without support for children from the five longitudinal studies in which information had been collected concurrently and with the same technique The number of children in the individual samples ranged between 152 and 272. In all the samples the cumulative distribution of the age of first walking described a practically straight line between the 5th and the 95th percentile on a logarithmic scale indicating normality

The age of first walking did not differ by social group or by sex in any of the samples Significant differences were found on the other hand between the median ages for each of the five samples Conceivable causes of this were discussed, e g genetic factors feeding conditions and the way the parents cared for the child.

CHAPTER IX

NON-NUTRITIONAL SUCKING IN AGES FROM INFANCY UP TO 6 YEARS OF AGE.

DEFINITION

The activity of sucking described and analysed in this essay comprises the sucking of fingers or a comforter without involving the assimilation of food.

MATERIAL AND METHOD

Data forming the basic material for studying the part of non-nutritional sucking has been taken from interview form VI items 11 12 and 13 for the ages of 1 - 6 months items 11 and 12 for the ages of 9 months - 5 years and in form V item 32 for the ages of 6 - 8 years

The habitual characteristics of sucking and the efforts of other persons to stop the habit have been estimated at every examination from the age of 1 month and up No occasionally" and definite habit are the degrees by which the group with a daily frequency are distinguished from the more occasional and from those without any extra sucking activity A child, who every night before falling asleep puts his thumb in his mouth has been noted as definite habit even if the activity mainly or solely is connected with this occasion. Data on the intensity of the habit are available at the ages of 1 - 6 months and 4 - 5 years The efforts of other persons to put an end to the occasional or the habitual behaviour have been graded into none mild, or intensive

Concerning the construction of the variables and the items forming part of the statistical tests of significance to illustrate the habit of sucking the reader is referred to the later parts of the presentation where etiological theories are tested (page 39) and the connection between the prolonged habit of thumbsucking and emotional symptoms is illustrated (page 45)

FREQUENCY

Result

The occurrence of the stated behaviour according to crossectional analyses made at different ages is illustrated in the frequency graphs fig 1

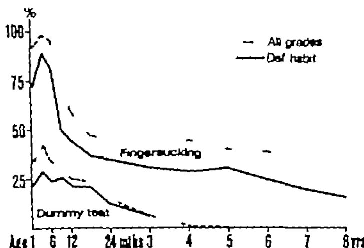


Fig 1 Incidence of finger/comforter-sucking at various ages Percentage distribution. Crossectional figures

Practically all children in the sample resorted to non-nutritional sucking during their infant year More than half of the girls and two-thirds of the boys had stopped sucking their fingers at the age of 18 months The frequency curve declined steeply during the latter part of the infant year This coincides with the periods when sucking is used less and less for feeding The teething period has started and the child receives a growing proportion of solid food

After this time and throughout the pre-school stage there is only a slow reduction in the number of fingersuckers Of the 78 children who at the age of 18 months had developed a definite habit of finger-sucking 80 % still resorted to some kind of fingersucking at the age of 6 The corresponding figure at the age of 8 was 61 %.

The 5-year-old fingersucker for example is more seldom a child who has relapsed into a previous habit In most cases the child had the habit all the time Only a quarter of the cases in the ages 3 - 5 was an irregular and periodical practicer of the habit

The frequency curve of comforter-sucking showed much the same form as that of fingersucking though at a lower level (fig 1) On the average the comforter-sucker abandoned this habit far earlier than the fingersucker At the age of 1 year 25 % of the children still used a comforter habitually while only a few percent still did so after the age of 4

Few children resort solely to comforter-sucking initially Contemporaneous fingersucking may ever be intensive but those who practiced both habits made up only 26 28 and 19 % at the ages of 1 3 and 6 months respectively The frequency of this contemporaneous sucking reached a peak between the ages of 3 - 6 months irrespective of intensity Later during the second half of the infant year there was a stronger reduction of thumbsucking than of comforter-sucking in addition to a general decline of sucking activity Even if the child after a time of contemporaneous comforter-sucking chose the thumb the fixation to the thumb generally lasted a shorter time than if he had resorted to thumbsucking only

For the intensive thumbsuckers at 3 months of age combined with habitual comforter-sucking the median age for the cessation of all sucking activity in question was 28 1 months The corresponding age for intensives without comforter-sucking was 62 5 months The difference according to the median test is significant at the 2 % level

Evidently it is not just a coincidence that only 2 out of the 59 children who used a comforter up to the age of 1 year came to belong to the group of fingersuckers practically throughout pre-school age Only 3 % of the habitual 5-year-old fingersuckers had used a comforter during their infant year; the others had started directly with fingersucking The probability of the difference being due to chance is very slight

Discussion

In this sample fingersucking comforter-sucking or a combination of the two are so frequent during the first part of the infant year that they cannot be described either as "bad habits or as unusual ones This frequency indicates a need of sucking either inherent or learned which is not sufficiently satisfied by nutritional sucking Sucking activity reaches a peak during the first 6 months After a steep decline before the age of 1 the frequency curve displays a quite different gentle slope during the following years This could be interpreted as a sign of different sets of reasons during the infant year as compared with a later age The frequency curve is in agreement with Benjamin s suggestions following experiments with monkeys that thumbsucking could begin for one set of reasons and be sustained for others (1) Evidently the non-nutritional sucking which occurs for example at the age of 3 months has a rather uncertain predictive value concerning sucking activity in the pre-school stage However a habit of fingersucking which has been developed at the age of 1½ years is very difficult to get rid of In most children it remains for several years. Finger sucking as a symptom is strikingly constant but the same is not as true of comforter-sucking The cause of the difference can only be presumed. The simple fact that the thumb is more accessible than a comforter may guide development of the habit Once established, the habit of comforter-sucking finds no replacement in fingersucking when it comes to an end.

SEX DIFFERENCES

Result and discussion

Finger-sucking is in this sample from the age of 12 months much more frequent with the girls than the boys In table 1 is seen the χ^2-values for sex-differences in fingersucking

Table 1 Sex-differences in various ages

Chi square comparison p = probability level

Age	χ^2	p
1 month	negligible	-
3 months		-
6		-
9		-
12	4 505	05
18	5 056	025
24	8 872	005
3 years	4 621	05
4	7 868	005
5	9 183	005
6	9 351	005
7	12.653	001
8	9 399	005

At every age level examined, from 1 year up to 8 the difference is statistically significant or probably significant which corresponds to the stability of the habit If the group of habitual comforter-suckers is combined with the group of habitual finger-suckers the sex difference at 12 months still shows that the girls resort to extra sucking more commonly than the boys (χ^2 = 3 671) It is not clear whether this difference is real or illusory inherent or conditioned. Marjorie Honzik (11) who has studied the literature in this field and participated in one of the longitudi-

nal California studies points out that the information concerning sex differences is contradictory for one thing because of the combination of ages in the material examined The distinct sex difference observed by her in children of pre-school age is according to her a real sex difference concerning sensibility and satisfaction of tactile stimulations

Naturally a child s early sucking activity is mainly connected with nutritional sucking For a whole lot of children evidently this sucking is enough as a source of satisfaction at least at the time during the second part of their first year when the need is decreasing If all kinds of sucking activity at the age of 12 months including nutritional sucking are combined in the previously mentioned test on different sucking behaviour in boys and girls the statistical sex difference disappears The total number of children with some kind of sucking either conditioned by feeding or occurring as extra sucking of fingers or a comforter is divided rather evenly between the sexes (X^2 = 0 139) Neither is the sex difference significant if the same calculation is made at the age of 2 on the basis of information on conditions between the ages of 1½ and 2 (X^2 = 2 173) Later on however when nutritional sucking has ceased, the girls greater frequency becomes manifest

It has been pointed out (13) that the boys in this sample were breastfed longer and also bottlefed longer than the girls If a certain period of time is of importance for learning or developing the habit for example at the end of the first year when nutritional sucking is decreasing the girls more than the boys run the risk of being fixed to the need of extra sucking According to the reasoning presented here the sex difference observed might well be due to differences in the way the practice of feeding has developed.

ETIOLOGICAL VIEWPOINTS

INTRODUCTION

The sucking activity of an infant is mainly connected with the satisfaction of its nutritional needs Therefore the relation of extra sucking to the feedinghabits of the children has a strong bearing on etiological considerations This applies to the origin of the habit of fingersucking but it hardly considers the fact that the child sustains the habit After infancy the comforting function seems to dominate Some children find satisfaction in fingersucking or in comforter-sucking when going to sleep when worried or when they just want to increase their well-being

All the issues introduced in this section touch on the two contradictory hypotheses mentioned in the introduction, the psycho-analytic one and the one which claims extra sucking to be a product of learning The information from the mothers at the longitudinal follow-up should be fairly reliable since the intervals between examinations have been rather short It is not probable that the child s changing behaviour at feeding can have made the mother remember or interpret things erroneously which otherwise might be the case

Material and method

Finger/comforter-suckers with a habit of at least 3 years have been compared with the rest of the children in the sample with respect to: the kind of feeding different times for weaning from the breast and for the cessation of all nutritional sucking the degree of satisfaction at a meal crying the length of a meal and anxiety before a meal Finally the intensity of habitual extra sucking in the infant at no more than six months has also been used to illustrate the prediction of the maintenance of this habit

The items concerning feeding which have served as a basis for the comparison have been taken from form V Concerning the issues connected with items 34 - 41 there is information from every examination about the number of breastmeals and bottlemeals a day Items 34 and 38 deal with the time of weaning from the breast or the bottle Sucking is involved in both kinds of feeding and since the method of feeding does not seem to influence the frequency of fingersuckers (see below under Result) the more meaningful term nutritional suckers has been used to cover both. The age at which nutritional sucking ceased has been established.

Item 32: 7 8 9 gives information about the observations and complaints related by the mothers concerning meals The child may not have been satisfied at the meal it may not have wanted to stop eating or it may have eaten too fast; in other words the observations concern something remarkable at the end of a meal

The average time of sucking at meals varies from child to child. Even if the mothers information about how long a meal lasts is approximate there must be a considerable difference between the extremes The grading in minutes is given in item 52.

The child s anxiety before a meal has been estimated by the mother in stating the number of minutes that the child usually screams before it is given the breast or the bottle This is naturally a discretionary judgment which has certain limits concerning exactness. Still the information ought to indicate different degrees of frustration between the children who are left to scream (> 10 minutes) and those who keep waiting happily or with a slight degree of irritation (item 63:0 7 8 9)

Information about the intensity of the fingersucking habit during the first 6 months is to be had in form VI, item 11:0 - 5)

Result

The results from the significance tests are compiled in table 2 The feeding situations used in the comparison between the 5 year old habitual suckers and the other children are listed as variable headings

Table 2. Feeding conditions of finger/comforter-suckers (> 3 years duration) versus those of non-suckers

Variables	χ^2	p	Number of children in group
1 Early bottlefed (from before 2 mths) /others	negligible	n.s	n = 209
( ) /breastfed >6 mths (extremes)			n = 142
2. Weaned from the breast before/after 4 mths ♀			n = 88
♂			n = 121
6 ♀			n = 88
♂			n = 121
between 1 – 3 vs others ♀			n = 88
♂			n = 121
" 2 – 4 vs others ♀			n = 88
♂			n = 121
2 – 5 vs others ♀			n = 88
♂			n = 121
from nutritional sucking			
before/after 9 mths	6 370	02	n = 209
/ 12	4.169	05	n = 209
4 Satisfied at meals at 1 and 3 mths/others	7 167	01	n = 209
1 3 and 6 mths/others	5 642	02	n = 209
5 Duration of sucking at a meal at 3 mths long suckers/short suckers	4 191	05	n = 91
6 Crying long before meals at 3 mths as well as 6 mths/others	negligible	n.s	n = 209

Ad 1. Bottle- and breastfeeding Finger/comforter-suckers whose habit lasted at least 3 years did not differ from other children concerning bottle- or breastfeeding during the infant years Those who had been fed mainly with a bottle became fingersuckers to the same degree as the others Nor was there any obvious difference between bottle-children and late-weaned breast-children i e those who had been given breast-meals up to 6 months or longer Hanna (9) has newly reported much the same

Ad 2. Weaning from breast Weaning from the breast with the loss of an assumed better psychological climate has been held to be of great importance as a cause of fingersucking (12) The test scores for groups weaned at different times do not confirm the idea that the cessation of breastfeeding as such influences the existence and persistence of fingersucking Nor is the assumption reasonable that a certain period of weaning (for example between 2 and 4 months) involves a greater risk of adopting a certain behaviour than other periods of weaning (23)

Ad 3. Weaning from nutritional sucking For a about one quarter (54 children) of the more than 200 children nutritional sucking ceased before the age of 9 months Among these children finger/comforter-sucking up to at least 3 years occurred comparatively more frequently than among those who had been weaned after 9 months The statistical test is significant at the 2 % level When the limit for the cessation of nutritional sucking is set at the age of 12 months the test gives a response at the 5 % level The chances of satisfying a well-established need for sucking are naturally greater during a longer period of nutritional sucking According to the learning theory however (see below) a longer period of sucking would also increase the chances of fixating the need It i therefore noteworthy that out of the 21 children of both sexes who between the ages of 2 - 3 years still received one or more sucking-meals a day (one was still breastfed) only 3 belonged to the group of comforter-thumbsuckers with at least 3 years of habitual sucking (X^2 = 6 012 p = 02)

Ad 4. Satisfaction at meals At the examinations during the first 6 months (at 1 3 and 6 months) the mothers stated that 36 children

were more or less unsatisfied when they had stopped eating 20 of these children later belonged to the group of finger/comforter-suckers The probability of a sucking habit developing seems to be significantly greater if the child has displayed symptoms of discontent or dissatisfaction at the end of a meal than if it has been classified as satisfied.

When only the conditions at 1 and 3 months are taken into consideration, the difference becomes even more marked (X^2 = 7 187 p = 01)

Ad 5, The length of a meal The graph showing the average duration of a meal with children of 3 months of age suggest that this function is normally distributed The 20 % short-suckers have been compared with the 27 % long-suckers Those in the second group resort less to prolonged extra sucking of at least 3 years (p = 05)

Ad 6, Crying before meals Incitements to extra sucking should be more frequent in the crying group than in the patient one The children who have been noted as crying more at the ages of 3 and 6 months stop their thumb/comforter-sucking before the age of 3 years just as often as the others Nor is there any apparent connection between prolonged crying while waiting for food and intense thumb-sucking at the age of 3 months (X^2 = 0 556 p = no signif)

Early intensity of the habit About as large a proportion of boys as girls have been noted to be intense thumbsuckers This applies to the ages of 1 3 and 6 months and the number of intense suckers increases significantly with both sexes (X^2 = 16 68) between 1 and 3 months Between 3 and 6 months there is only a slight increase the frequency amounting to 48 % of the girls as well as of the boys at 6 months

A significance test concerning the intensity at an early age and a later habitual sucking has been performed with the girls in one group and the boys in another The girls who were judged by their mothers to be intense thumb- or comforter-suckers at either 1 3 or 6 months featured no more frequently than others in the group who were still habitual suckers at the age of 3 years As regards

the boys there is a probable significance that those who had been intensive suckers at 3 and 6 months respectively continued to suck at least up to the age of 3 years while most of the non-intensive ones had stopped. The intensity at one month of age did not make any difference to the frequency of extra sucking at the age of 3 years

Discussion

Concerning the discussion of the accumulated results of relations to feeding the reader is referred to the general discussion on page 54

PROLONGED FINGERSUCKING (> 5 YEARS) IN RELATION TO EMOTIONAL SYMPTOMS

INTRODUCTION

The habit of fingersucking slowly disappears during pre-school age and the first years of school and it may be asked why this infantile sucking manifestation persists so much longer in certain children than in others Even though, as illustrated the continuation of sucking as an expression of a need for comfort may have a possible influence Indications of an increased need of comfort will be examined with the following questions: Does the group of children with prolonged fingersucking display any stress factors which may distinguish this group from the non-suckers? Have the fingersuckers any accumulated symptoms of psychological imbalance during the pre-school stage which cannot be found in others and which would indicate a connection with an environmental influence?

Method

To illustrate these questions the group of 62 children (38 ♀ + 27 ♂) who sucked their fingers up to at least 5 years of age has been tested against another group in the sample with respect to certain psychological psychosomatic and social variables according to Table 3

Children with appetite troubles are those who have been said to have a bad or not-so-good appetite at (a) half of the examinations and (b) more than half of the examinations from 1 to 5 years of age (Ta 36: 6 7)

The variable "Night disturbances refers to (a) poor sleepers up to 3 years old (groups IV and V according to the definition in the essay on sleep behaviour in Acta paed. (15) and (b) children who have often, at 4 and 5 years of age woken up in a state of emotional anxiety

The variable Stuttering" refers to all kinds of nonfluent speech disturbances The answers to the question "Does he stutter at all? have been divided into "no occasionally" and often The degree of speech disturbance has been determined from the child s condition at two of the three examinations between 3 and 5 years of age In a 6-column table a comparison has been made between children with and children without fingersucking

Opinions about sensitivity and liveliness in the children have been divided into three degrees: sensitive - medium - stable and lively - medium - quiet respectively At the ages of 3 or 4 there is no sex difference in this behaviour The children who have been conside-

red quiet amount to only a little more than 10 % There is no obvious connection with fingersucking

The occurrence of destructiveness in children divided into never occasionally" and definite habit is a definitely sex-divided characteristic at 3 as well as 4 years of age (see ch. XV) The boys predominate in a statistical comparison on at least the 1 % level Special calculations have therefore for boys and for girls been made with respect to the connection with fingersucking The result showed no significant connection with either group The figure in the table refers to both sexes

In the correlation to the mother s employment the children of mothers who have been employed at all during the child s first 3 years have been compared with regard to fingersucking to those whose mothers have not been employed during this time

Result

The results of the significance test are summarized in table 3

Discussion

As the table shows of all tested variables only the mother s employment gives a result in the statistical test The children whose mothers are housewives are significantly more common among the fingersuckers than the children of employed mothers Since fingersucking is partly an evening habit not even a full-time employed mother could be p observing it The children of employed mothers generally have a more extrovert life and more contacts with others Fingersucking has been regarded as a simple reaction to boredom tiredness disappointment and punishment i.e the habit is used as consolation. Those who become fixed to this habit of satisfying themselves early or oft n continue to do so for years There is nothing however which indicates that the fingersuckers up to the tested age have a stronger need for consolation in comparison with others and that fingersucking consequently should be one symptom among others of a general emotional lability or of a disturbed personality development For most children the pre-school age is filled with troubles There are many ways of trying to escape troubles and find satisfaction. Some children seek their satisfaction in fingersucking others elsewhere Those who are come to like the sensuous oral sensations or have grown accustomed to a certain behaviour find it difficult to give it up Fingersuckers are no more than others characterized by stress-symptoms or by any

Table 3 *Psychological and social variables in fingersuckers* whose habit lasted at least 5 years in relation to others (n = 204)

Variable	Interview form Nr item and dig	χ^2	p
Appetite troubles 1-5 years			
a) at half of the examinations	V: 31: 6 7	negligible	n.s.
b) at >	V: 32: 6 7		
Troubles with weaning from nutritional sucking	V: 57-58: 7 8		
Sleep disturbances:			
Resistance at bed-time at 3 years	VI: 55: 8 9		
Night waking 9 months - 3 years	VI: 61 o 63-66		
with anxiety 4 - 5 years	VI: 61:7-9 o 62:4 5		
Speech disturbances:			
Stuttering 3 - 5 years	V: 67: 8 9		
Tics (of all kinds) at 4 or 5 years	VI: 20: 4-9		
Nailbiting (of all degrees) 2-5 years	VI: 13: 4-9		
Sensitivity at 3 years	VII: 76: 7-9		
Liveliness	VII: 75: 6-9		
Destructiveness at 3 years	VII: 58: 8 9		
) - - - - - - - - - -			
Sisters or brothers before the age of 3	O: 17		
Social gr Graffar modif at 3 years	O:76: 1-5 (longitudinal)		
The mother s education when the child is 3	O:80: 1-5	4 895 (2df)	
Housewife / employed during the child s first 3 years	O:20: 1-4	7 106	01

other kinds of behaviour that characterize children with difficulties in adjusting themselves or children with psychological problems

S E Q U E L A E O F F I N G E R S U C K I N G

FINGERSUCKING - MALOCCLUSION

Introduction

Those who have studied fingersucking and its consequences are now agreed that attention should be focussed on its effect on the jaws and teeth. In the 1920 s malocclusion was a bogey which made many parents dentists and pediatricians heavily oppose the habit of fingersucking. They tried to cope with the problem, using various ingenious means of compulsion. The reaction which followed referred among other things to longitudinal studies of anomalies of the bite which gave a less rigid picture of the causes (5 4) Malocclusions have many causes only one of which is finger/comforter-sucking Moreover even an habitual thumbsucker can have an adequate occlusion (17) To find out to what extent the children in this sample have developed malocclusions as a consequence of finger/comforter-sucking contact was established with the Institute of Orthodontics at the Royal Dental College in Copenhagen, where there is an intimate acquaintance with these problems. Studies have been made on the occurrence of malocclusions in several races with different sucking habits or no such habits at all (3 4 10) Investigations have also been made into the functions of the tongue and the lips in children with sucking habits Thanks to their courtesy 136 of the children in the sample (those who could be present on this occasion) at ages between 9 and 12 years have been examined at various stages of eruption of their second dentition.

Result

Briefly it can be said that in the groups with sucking habits (prolonged fingersucking and comforter-sucking) 13 % more than in the groups with minimal or no sucking were registered as having symptoms of malocclusion. The difference is not statistically significant ($\chi^2 = 2.498$) but even considering special anomalies it points consistently in the same expected direction. For example there was an increased occurrence of extreme maxillary overjet and of open bite in the group of finger/comforter-suckers and furthermore a higher frequency of deep bite among early comforter-suckers Distal molar

occlusion was most common among the fingersuckers while mesial molar occlusion occurred more often among the comforter-suckers The groups are too small to give a reliable statistical result~ It should be noted that 6 of the children with prolonged thumbsucking and 2 of the 9 most persistent comforter-suckers were free from symptoms

Discussion

An absence of symptoms is thus compatible with habitual extra sucking Certain occlusal anomalies are furthermore conditioned by development and relatively common during growth (3 9) Renewed examination of the bite after puberty in the material as a whole is expected to give information on the degree to which the physiological tendency to normalization is made more difficult by prolonged sucking

FINGERSUCKING - ARTICULATION TROUBLES

Introduction

Articulation defects are possible consequences which have rarely been discussed (27) The pronunciation of consonants might be sensitive to deviations in the positions of the teeth and jaws of the tongue and the lips The relative frequency in the groups with different sucking activities during the period of speech development ought to indicate to what extent these divergences are reflected in articulation troubles

Method

Such a judgment has been applied in the present material to children at 4 and 5 years of age This age was chosen with regard to ordinary speech development which is considered to have reached maturity in enunciation at this time (see essay on speech development) The articulation defects have been exemplified by the mothers. The information is derived from form V: item 68: 1 3 5 It is mainly concerned with lisping and other difficulties with the s sounds (26 cases) and the r sound (8 cases) There are also some children who find it difficult to pronounce v f t and k. A combination of defects in the pronunciation of consonants is not unusual No detailed phoniatric analysis of the defects in articulation has been included in the study

Result

Table 4 shows a relatively higher frequency of pronunciation defects in children with prolonged fingersucking than in others The difference between the groups is statistically significant both concerning articulation defects in a wider sense including lisping (p = 01) and concerning lisping only (p = 025) These articulation defects at 4 or 5 years of age which have been observed by the mothers tend to disappear when the child reaches school age In 8 out of 20 children who had dyslaly as well as prolonged sucking at 4 and 5 years of age a noticeable articulation defect remained during their first year of school Nearly all the 20 children were still thumbsuckers when they started school. 5 children remained out of the other 20 with stated pronunciation defects At 8 years of age there is still a tendency though not statistically significant for some slight discrepancies in pronunciation to be more common among habitual fingersuckers than among the other children.

Table 4 Faulty articulation and lisping among fingersuckers and others

	n	Articulation errors at 4 or 5 (except lisping)	Lisping at 4 or 5 yrs
Fingersucking 5 years	65	10	10
Others	139	12	8
Total	204	22	18

PARENTAL REACTION

Introduction

Observations in connection with forced weaning from fingersucking have raised the question of whether disturbances in the children s psychological balance are a consequence of such weaning Bedtime troubles night waking increased screaming increased obstinacy bed-wetting and general symptoms of discomfort have been reported (15) The question related here is to which extent parental reactions on fingersucking nowadays do exist

Method

A systematic registration has been made of the parents measures against extra sucking of this kind from 1 up to 5 years of age but unfortunately not beyond that The attempts to stop the habit mostly consist in telling the child to stop and promising him something extra if and when he does. The measures which have been classified as intensive are: consistent threats with a frightening touch, for example that hands and nails will be disfigured that the thumb may fall off that "bad germs will get into the stomach.

Result

Mothers attitudes towards the sucking habits of children are nowadays characterized by tolerance The attempts to stop fingersucking or comforter-sucking up to the age of 3 are mostly very mild. Corporal punishment has been reported only in one case where the father hits the child and the grandmother threatens to backbind him, while the brothers and sisters insult him.

The worries that sucking may bring about difficulties increase if the habit persists to a higher age "Intense attempts at weaning have been made on a few children at the ages of 4 and 5 without any immediate results The 4 children subjected to what have been noted as intense attempts were still fingersuckers at the age of 7 and 3 of them were still habitual suckers at the age of 10 They include the maltreated child mentioned above

Equally bad results are yielded by a comparison between the fingersuckers aged 4 and 5 years upon whom only mild attempts have been

Table 5 Measures against fingersucking at different ages calculated on the number of children with fingersucking (occasionally + definite habit)

Age in months	Mild attempts %	Intense attempts %
12	1 6	
18	3 2	
24	9 7	
36	20	1
48	25	
60	31 6	5

made to stop the habit and a similar group which has been left alone The two groups have much the same percentage of fingersuckers at the age of 8

The mother s education has not been of any significant importance when deciding whether or not measures should be taken (χ^2 = 1 247)

Discussion

Evidently information about the ineffectiveness of using coercive measures has reached mothers of different levels of education The vast arsenal of mechanical aids for stopping infant thumbsucking which was described 20 years ago (15) is no longer to be found.

GENERAL DISCUSSION

Contradictory facts concerning the etiology of the origin of thumb-sucking and its persistence can be had from the literature Compared with all the reflections about its consequences there are remarkably few experimental or analytical facts to support any hypotheses about its origin. According to psychoanalytic theory thumbsucking is an autoerotic activity and the lips are an erogenic zone (7 12) Sucking in connection with eating and the abatement of hunger gives a satisfaction which is transformed to be associated with the act of sucking According to the theory of learning which has grown stronger in the last few years (1) the congenital suckingreflex can be awakened to different degrees depending on the intensity and persistence with which it is exercised Prolonged thumbsucking is regarded as a product of learning which has been conditioned by its original pleasant association with food and care (20 28) Consequently there is an intensification of the normal sucking reflex through repetition unconnected with feeding If this intensification is stopped by the infant s wearing mittens every day at special hours during the first months as in Benjamin s study (2) the result is that fingersucking later occurs much less frequently among these infants than among the controls According to this hypothesis the hours when fingersucking is to be made impossible are when the rooting and placing reflexes are maximal This occurs when the child is hungry or when it is put to bed in such positions that the hands can easily touch the cheeks and mouth. It has been shown (6 8) in 1948 that some children who were fed with a cup instead of a bottle or the breast never developed sucking reflexes of any noteworthy intensity Under these circumstances it seems strange that no statistical connection between the anxiety of hunger (crying) and thumbsucking could be established in this study There is better correspondence with the statements by Korner et al (16) in 1968 after direct observations of bottlefed new-born babies that only mouthing (different movements of the mouth) was significantly hunger-related while fingersucking a hand-to-face and a hand-to-mouth activity lacked any observable connections At this early age however a deliberate movement of the hands towards the mouth is physiologically impossible in which case the touch would be conditioned by the situation.

According to the theory of learning it is also difficult to explain why children with both an intense fingersucking and an habitual *comforter-sucking stop with either or both at a considerably* younger age than those who have resorted to intense fingersucking only The stronger use of sucking ought to give the *opposite* result It is also difficult to explain why children who suck longer at meals become fingersuckers less often than those who suck for a shorter time Roberts (22) has reported findings in the same direction. What is easier to explain however is that the children who have been classified as being satisfied at meals do not need any extra sucking.

The stimulus limen to induce a sucking reflex is lowered at hunger Everything that touches the area around the mouth and cheeks seems to make the child move its mouth and turn its head towards the object A touch on the lips induces sucking movements Evidently this series of mutually related reflexes has a practical purpose In the *light of these facts it is therefore* not *at all sensational nor is* it difficult to interpret that practically all children in this sample (all nutritional suckers) have been noted as resorting to some kind of extra sucking at 3 months of age From a preventive point of view it is more important to know why the fingersucking in a larger group of children persists beyond the age when sucking activity is normally reduced. A longitudinal study is in a better position to illustrate this than other studies but even so it has not been possible to present a convincing comprehensive explanation.

One thing is evident however that the thumbsucking child of preschool age may have or lack emotional stress symptoms to the same degree as his non-thumbsucking peers It should also be noted that Tryon (29) in his test (The Childrens Manifest Anxiety Scale) has not been able to show any differences in symptoms of anxiety Observations and reports that fingersucking is indicative of emotional disturbances (12) have probably been based on individual cases. It is also possible that a part may be played by the children s inherent differences of temperament differences in their sensibility towards stimulation of the lips or differences in their demands for satisfaction of needs The observation that those who are inten-

as suckers from the very beginning (this applies only to boys) are likely to develop prolonged sucking can just as well be interpreted this way as being a sign of learning

As a basis for an explanation it is not enough to regard thumbsucking as a product of learning. The weaknesses of the theory become evident when the development and disappearance of the habit in a group of children is observed in relation to feeding conditions Only a small number of the children with real prolonged thumbsucking come from the group who were both thumbsuckers and comforter-suckers in infancy although one might suppose that these children would run a greater risk of developing a need for sucking

SUMMARY

The origin, frequency and gradual decrease of the habit of fingersucking during the first 8 years have been studied in 212 children involved in a longitudinal study of growth. This extra sucking of the whole group stops at a median age of 12 9 months Comfortersucking in combination with intense fingersucking at 3 months results in a significantly lower median age (28 1 months) than does fingersucking alone (62 5 months) A fingersucking established at the end of the infant year decreases very slowly

A sex difference with a significant dominance of girls becomes evident on each level from 1 to 8 years It is possible however that the time of cessation of nutritional sucking which is relatively late for the boys in this sample may determine the indicated sex difference

Significance tests were made of the correlation between fingersucking and the mode of feeding Breast- or bottle-feeding makes no difference but the time of cessation of nutritional sucking the duration of the sucking meal and the satisfaction at this meal are inversely correlated to prolonged thumbsucking in a way which cannot be coincidental

Eleven psychological and four social variables have been significance-tested in their relations to the prolonged sucking habit and are illustrated in tabular form. It has not been possible to prove that emotional stress symptoms distinguish long-term thumbsuckers from others Housewifes have more fingersuckers than mothers gainfully employed during early ages of the children.

The effects of habitual fingersucking with respect to malocclusion and articulation defects have been studied. Slight discrepancies in pronunciation occur significantly more often in 4 - 5 year old thumbsuckers than in others In the group with sucking habits 13 % more children had symptoms of malocclusion than in the group with minimal or no sucking The difference is not statistically significant but even concerning special malocclusions it always pointed in the same direction.

REFERENCES

1 Benjamin Lorna S : The beginning of thumbsucking Child Development 38:1065 1967

2 Benjamin L.S and Mason W A.: Effect of hunger on non-nutritive sucking in infant rhesus monkeys J comp physiolog psych. 66:526 1963

3 Björk A.: Käkarnas tillväxt och utveckling i relation till kraniet i dess helhet Nordisk klinisk odontologi Bd I 2:a uppl Forlaget for Faglitteratur København,1965

4. Björk, A. Krebs Aa and Solow B.: A method for epidemiological registration of malocclusion Acta odontologica scand. 22:27 1964

5. Bowden, B.D : *A longitudinal study of the effects of digit- and dummysucking* Am. J Orthodontics 52:887 1966

6. Davis H. Sears R. Miller H.C and Brodbeck A J : Effects of *cup* bottle and breastfeeding on *oral* activities of newborn infants. Pediatrics 2:549 1948

7 Freud S : Three contributions to the theory of sex. In Brill A.A., editor: The basic writings of Sigmund Freud, New York Random Inc 1938 book III

8. Fredeen R.C : *Cup-feeding of newborn infants.* Pediatrics 2:544 1948

9. Hanna, James: Breast feeding versus bottle feeding in relation to *oral habits J of dentistry for children* 34:243 1967

10 Helm, S.: Prevalence of malocclusion in relation to development of the dentition. Acta Odontologica Scandinavica 24: suppl 58, 1970 Thesis

11 Honzik, M. and Mo Kee J : The sex difference in thumbsucking *Journal of Pediatrics 61:726* 1962

12 Kaplan M.: A note on the psychological implications of thumbsucking. J of Pediatrics 37:555 1950

13 Klackenberg G and Klackenberg-Larsson I.: Breastfeeding and weaning Acta Paediat Scand. Suppl 187:94 1968

14. Klackenberg G : The sleep behaviour of children up to three years of age Acta Paediat Scand. suppl 187:105 1968

15 Klackenberg G.: Thumbsucking: *frequency* and etiology Pediatrics 4:418 1949

16 Korner A et al: Organismic determinants of spontaneous behaviour in neonates. Child Develop. 39:1145 1968

17 Lundström A.: How much can we hope to reduce the incidence of malocclusion through prophylactic measures? The Dental Practitioner IX, 8 129 1959

S U M M A R Y

The origin, frequency and gradual decrease of the habit of finger-sucking during the first 8 years have been studied in 212 children involved in a longitudinal study of growth This extra sucking of the whole group stops at a median age of 12 9 months Comforter-sucking in combination with intense fingersucking at 3 months results in a significantly lower median age (28 1 months) than does fingersucking alone (62 5 months) A fingersucking established at the end of the infant year decreases very slowly

A sex difference with a significant dominance of girls becomes evident on each level from 1 to 8 years It is possible however that the time of cessation of nutritional sucking which is relatively late for the boys in this sample may determine the indicated sex difference

Significance tests were made of the correlation between fingersucking and the mode of feeding Breast- or bottle-feeding makes no difference but the time of cessation of nutritional sucking the duration of the sucking meal and the satisfaction at this meal are inversely correlated to prolonged thumbsucking in a way which cannot be coincidental

Eleven psychological and four social variables have been significance-tested in their relations to the prolonged sucking habit and are illustrated in tabular form. It has not been possible to prove that emotional stress symptoms distinguish long-term thumbsuckers from others Housewifes have more fingersuckers than mothers gainfully employed during early ages of the children.

The effects of habitual fingersucking with respect to malocclusion and articulation defects have been studied. Slight discrepancies in pronunciation occur significantly more often in 4 - 5 year old thumbsuckers than in others In the group with sucking habits 13 % more children had symptoms of malocclusion than in the group with minimal or no sucking The difference is not statistically significant but even concerning special malocclusions it always pointed in the same direction.

CHAPTER X

N A I L B I T I N G

N A I L B I T I N G

INTRODUCTION

Kanner asserts in his textbook (5) that nailbiting is an expression of emotional tension and that it is the most widespread of habitual manipulations of the body among children. Yet curiously enough, we also read that this widespread habit was regarded at the turn of the century as an exquisite psychopatic symptom or as a sign of degeneration (ibid.) Nowadays nailbiting in itself is never the *occasion of a clinical examination. Insofar as it is* accompanied by other nervous traits and symptoms of maladjustment it has come to figure as a sub-symptom in child psychopathology But experience gives us every reason to suppose that the phenomenon is an everyday problem of childhood rather than an indicator of any seriously disturbed psychic relations The frequency and persistence of the symptom together with its covariation, if any with other emotional symptom variables have however been considered worth examining using data from the 212 children of the longitudinal study

Method

The incidence and intensity of nailbiting have been noted in interviews from 2 - 5 years (form VI: 13: dig 0 - 9) and from 6 - 8 years (questionnaire V: 33: dig 0 - 4) Data collected during the first of these periods have been concerned with the habitual nature of nailbiting (occasionally phenomenon or definitive habit) and the intensity of efforts made to put a stop to the habit

The information provided by the mother during the second period has *unfortunately been solely concerned with frequency (several times* daily often or daily sometimes seldom or not at all) The reaction of the child s environment to its nailbiting has not been described at this later age period.

RESULTS

Frequency

Fig 1 show the frequency of nailbiting expressed in cross-sectional figures between the ages of 2 - 8 years Since the graduations of the habit were given different names before and after 6 years comparisons for the entire observation period should relate to all degrees

of intensity taken together It will be seen that sporadic nail-biting at least becomes more common as children grow older

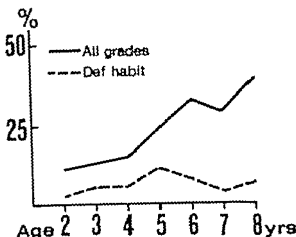


Fig 1 Incidence of nailbiting at various ages Percentage distribution. Cross-sectional figures

But the intensity varies If we only include those exhibiting the symptom daily nailbiting occurs in approximately 5 % when the children start school while approximately 15 % are occasional nail-biters. The rest up to nearly 40 % is seldom nailbiting

Sex differences

The symptom was consistently more common among girls than boys in this sample at every interview between 2 and 8 years At 5 and 6 years the tendency is so pronounced that a statistical significance of 01 and 05 respectively can be established.

Persistence of the symptom

Fig 2 shows the proportion of the sample who after first exhibiting the symptom at one age or another continued to do so to a greater or lesser degree at subsequent interviews Children reported as occasional nailbiters have here been taken together with those biting their nails daily The continuous curves which are superimposed on the cross-sectional frequencies (bars) represent children noted for nailbiting at every interview in the pure sample" The dashed curves show how frequently the symptom has recurred.

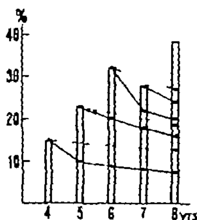


Fig 2 Persistance of nailbiting (all grades) 4 - 8 years of age

——— = persistent symptom at each investigation (pure sample)

- - - - = recurrent symptom at 8 years of age

Bars = frequency in cross-sectional pure sample at various ages

The most frequent grades also vary in intensity from one interview to another *Fig 3 (the left diagram) shows how children noted for* a definite habit at 4 years had changed one year later The right diagram in the same fig shows corresponding changes in daily nailbiters between 6 and 8 years

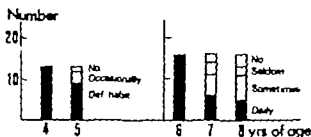


Fig 3. Changes in "definite habit" between 4 and 5 years of age and in "daily nailbiting" between 6 and 8 years of age

DISCUSSION

As can be seen from fig 1 the frequency figures differ considerably according to the gradation of symptom frequency on which the incidence of nailbiting is estimated Consequently there is little point in comparing frequencies with other cross-sectional investigations which do not generally have a similar division by grades of intensity Gedda (2) reports (1948) that he observed nailbiting in 7 % of children starting school (7 years) Jonsson and Kälvesten (4) found an approximate figure of 20 % in boys ages 7 - 16 years divided into a more or less equal number of moderately severe and slight forms Wechsler (7) who observed over 3 000 schoolchildren put the frequency of nailbiters at 36 %

Figures 2 and 3 show that nailbiting is a changeable symptom regardless of the degree of intensity noted at a particular interview The curves which denote the degree of permanence of the symptom, also indicate how once it has appeared a symptom can recur after a lapse of several years Thus nailbiting between 4 and 8 years is a symptom which varies in intensity in one and the same individual with longer or shorter periods when the symptom is either absent or only occurs to a negligible degree However if a child has chosen this mode of reaction at 4 - 5 years it is very likely to appear at subsequent stages of the observation period described here Children biting their nails at 6 7 or 8 years have had the same oral behaviour previously far more often than those who were not nailbiters at these ages

COVARIATION WITH OTHER VARIABLES

INTRODUCTION

The following hypotheses have been tested:

1) children who have stopped thumbsucking at 2 years or later have accordingly begun nailbiting

2) there is a tendency to covariation between temper tantrums and nailbiting

3) children noted for exceptional defiance symptoms bite their nails more than others

4) children with prolonged speech disturbances (recurrent proneness to stammering) or nervous twitches (tic symptom) are at the same time nailbiters to a notable extent

5) children with other forms of biting during early childhood will be nailbiters more than others

6) school start is related to deterioration of nailbiting

Method

Although nailbiting appears more or less periodically in the children in this sample one can distinguish a group of children in whom the habit persists year after year A group of 22 children (11 ♂ + 11 ♀) have been noted for the symptom at 5 or more of the 7 annual interviews between 2 and 8 years This group has been compared with the other children in certain respects

This group of persistent nailbiters has been used in certain of the above comparisons above all when testing covariations with other more permanent symptoms The other variables which have been employed are presented in the account of results

RESULTS

Relation to thumbsucking

Nailbiting is sometimes claimed to be a substitute for thumbsucking when the latter ceases The results derived from this sample do not indicate any probability whatsoever for such a connection The estimate has been made as follows: If the first report of the child nailbiting has been received in the same year as it stopped thumbsucking or the year after a connection has been assumed possible

Of the 106 children reported as nailbiting regardless of the degree of intensity at some point between 2 and 8 years there were only 12 whose abandonment of thumbsucking showed any conceivable chronological relation to the commencement of nailbiting. This proportion is within the limits of chance Fingersucking and nailbiting are not mutually exclusive Nailbiting can begin while a child is still fingersucking Nailbiters are not more predominant among those who stopped fingersucking before 5 years than among those who still suck their fingers (χ^2 = 0.906 n.s)

Relation to temper tantrums

In order to test whether children particularly noted for temper tantrums were notably in evidence among the group of persistent nailbiters those whose mothers had described them at 2 of 3 interviews between 6 - 8 years as particularly temperamental (V:62: dig 3 4) were compared with the others The result was a random distribution (χ^2 = 0 574)

Another test was also made concerning a possible covariation of temper tantrums and nailbiting Children noted for daily temper tantrums at 4 and 5 years (questionnaire VII: 54: 7-9) were tested for the occurrence of nailbiting during the three immediately succeeding years (between 6 - 8 years) The incidence was no more than coincidental The majority of the children included in the temper tantrums group had developed a more restrained disposition at this period between 6 and 8 years There was no notable increase in the frequency of nailbiting

Relation to defiance

Children considered particularly defiant by their mothers between the ages of 6 and 8 years (V: 50: 3,4) have been investigated regarding the incidence of nailbiting in the same way as those noted for temper tantrums Those considered most difficult at 2 of 3 interviews between 6 and 8 years (classified as often or always defiant when corrected) were compared with the rest The particularly defiant children included more members of the group of per-

sistent nailbiters than can be attributed to chance (X^2 = 4.587 p = 05)

Relation to stammering tendency or to tics

No such relation can be established. The variables employed for comparing covariation are enumerated in the essays on speech disturbances (page 142) and tics (page 207)

DISCUSSION

Temper tantrums are a typical age-related symptom. As they grow older children generally seem able to channel their tempestuous feelings over disappointments into more socially acceptable forms than bodily expression. Presumably those around the child show less disapproval of nailbiting than of the child lying on the floor and thrashing with its feet If the changes of temperament occurring between 6 and 8 years are an expression of self-control it is clear that nailbiting does not serve as a vicarious outlet for the emotions to any significant extent

The relation to defiance sheds an interesting light on the theory that nailbiting is a symptom connected with inhibited aggression directed against the child s own body The covariation is only probably significant Other causes appear to be involved. The situations in which a child or adult bites his nails are not as a rule consciously related to defiance or aggression but are more often than not described as a means of releasing emotional tension (1) The reasons for this tension can vary considerably and bear no apparent relation to an aggressive frame of mind. The influence giving rise to a symptom and converting it into a habit may be forgotten and the release which the habit provides may then be used for other reasons and purposes The analogy with the thumbsucking habit is by no means far-fetched. Probably it arises for one reason and then remains to be used in other contexts Nailbiting can be regarded as a functional automation, one of the original causes of which may lie in inhibited aggression.

Relation to other forms of biting

All prominent biting habits have been noted up to the age of 5 years These habits are for the most part an obviously aggressive symptom, but they also occur to a minor extent as expressions of play happiness and satisfaction.

The children noted for biting their siblings playmates or parents at various occasions or as a bad habit at 1½ - 5 years amounted to 83 = 41 % (30 ♀ + 53 ♂) The sex difference is not statistically significant At 3 years the figures for biting are 22 %, at 4 years 15 % and at 5 years 7 %

The covariation between nailbiting both of a temporary and a more persistent nature and biting of this kind in children between 1½ and 5 years has been tested (χ^2 = 0.443) Thus it does not occur in the same individuals more than one might expect from coincidence

DISCUSSION

The aggressive component in biting becomes more prominent with increasing age: at least this behaviour is interpreted as unfriendly by those who fall victim to it Whatever the frame of mind that prompts it be it playfulness aggression or defence biting produces a pain reaction which can easily elicit an aggressive response There are examples of siblings or playmates biting each other Generally however it is the adult (= the mother) who intervenes to punish, first by reproof or sending the child to bed or if the behaviour continues by corporal punishment Half the boys and a third of the girls biting in this way had immediately been administered corporal punishment Preventive or diversionary measures are reported less often. There is a striking difference between this reaction and the milder response to nailbiting (see page 70)

Assuming that nailbiting is an aggressive symptom (directed against the child s own body) one might expect theoretically speaking to find a demonstrable relation between aggressive biting and nailbi-

ting Nailbiting rises in frequency at the same time as aggressive biting declines as a result of development or of the pressure exerted by those around the child. The extroverted act of aggression is then forced into other channels in order that the child can attain the acceptance it seeks Nailbiting might be interpreted as a reserve channel of this kind for venting emotions of an aggressive natur The present investigation does not provide any statistical evidence for this assumption

Nailbiting seems to appear irregularly equally often or equally seldom in children who have or have not displayed a striking tendency to biting at 1½ - 5 years instead of occurring more frequently in the former category Although in individual cases nailbiting appears to be accentuated by conflicts between parents and children, the opposition displayed by parents to the habit is only one of many everyday situations capable of generating disappointment and emotional tension. Thus any relation is easily concealed. The evaluation of the personality tests may possibly provide a better basis for assumptions and reflections concerning the relation between aggression and nailbiting

Relation to school start

The diffuse tension which a child can experience when confronted by the strains of the first year at school have been regarded as a possible cause of nailbiting The frequency of the habit rises during the first years at school so that one is led to suspect a certain relation. If the symptom has appeared for the first time or become more regular i.e if a deterioration has occurred by the first interview after the child started school at 7 or 8 years the presumed relationship has been assumed probable If nailbiting previously established has disappeared or become less frequent this has been noted as an improvement Against this background the changes in connection with starting school noted for the 196 for whom adequate data were obtainable are as follows: deterioration 28 improvement 15 no change 153

According to the sign test the difference in number between the 43 children whose behaviour changed in one or the other direction is

just inside the 5 % confidence limit (see Documenta Geigy Scientific Tables p 105) In other words the only difference which can be established in this material is one which, notwithstanding its size may be coincidental

Children in the sample who were investigated within six months of starting school showed 14 deteriorations, 12 improvements and 88 no-changes with regard to nailbiting. Thus no definite rise in frequency can be observed in connection with this first period at school

PARENTAL REACTIONS TO NAILBITING AT 2 - 5 YEARS

Generally (= 80 %) mothers react to the behaviour even when the children are small and try by various means to cure them of it But the reaction is not particularly strong Of the total number of reactions noted up to the age of 5 years 92 % are classified as mild and 8 % as intense Even in cases where nailbiting is classified as habitual the reaction is still overwhelmingly mild.

Examples of attempts classified as intense include frightening corrections: "bad for your insides germs in your tummy" "ugly hands and nails "might have to go into hospital together with the purchase of a bitter-tasting substance (Finger-tip) painted on the nails or a rap on the fingers

These countermeasures did not meet with any notable success Deteriorations and improvements are fairly evenly distributed, regardless of whether any action is taken or not The following figures can be quoted: Of 86 children noted for countermeasures at 4 and 5 years 18 showed a deterioration 23 an improvement and 45 no change at all at the next annual investigation. Reactions to nailbiting in older children (over 5 years) have not been noted.

SUMMARY

The age frequency of nailbiting the persistence of the symptom and its covariation with other behavioural variables up to the age of 8 years are illustrated by material from the longitudinal Stockholm study Symptom frequency rises gradually during the pre-school years

to approximately 5 % daily nailbiting during the first year at school The frequency at the same age rises to c 40 % if less than daily frequencies are included (= all degrees of frequency)

Girls bite their nails consistently more frequently than boys The sex difference is statistically significant at 5 and probably significant at 6 years

During the ages observed nailbiting is often a more or less periodic symptom but once the symptom has appeared it has a definite tendency to recur

No statistically significant relations can be established between the cessation of thumb-sucking and the commencement of nailbiting nor between school start and deterioration in terms of nailbiting Children regarded by their mothers as particularly defiant between 6 and 8 years also tend more than other children to be nailbiters This was the only variable among those tested in which the result of the established covariation was hardly coincidental Tendencies to stammering tics or other oral sucking and biting behaviour were not related to nailbiting The measures taken by parents to induce children of 2 - 5 years to stop biting their nails are generally of a mild nature The action taken, generally in the form of verbal correction to which threats of fright may be added does not eliminate the symptom more often than abstention from any action at all The aggressive response elicited by biting another person is contrasted with the gentle reaction of parents to nailbiting

REFERENCES

1 Billig A.: Fingernailbiting: its incipiency incidence and amelioration Genetic Psychol Monograph 23-24:125 1941

2. Gedda E.: Studier över nervösa beteendestörningar hos skolbarn i de 4 lägsta klasserna. Sv Läkartidningen 50:763 1953

3 Hill G : Nailbiting Am.J Psychiatry 103:185 1946

4. Jonsson G and Kälvesten A.L.: 222 Stockholmspojkar Summary in English. Monografier utgivna av Stockholms kommunalförvaltning 26 1964

5 Kanner L.: Child Psychiatry 3ird ed. 1958 Thomas Publ New York

6 Pennington, S : The incidence of nailbiting among adults Am.J Psychiatry 102:241 1945

7 Wechsler P : The incidence and significance of fingernailbiting in children. Psychoanalytic Review 18:201 1931

CHAPTER XI

R H Y T H M I C M O V E M E N T S I N I N F A N C Y A N D E A R L Y C H I L D H O O D

R H Y T H M I C M O V E M E N T S I N I N F A N C Y A N D E A R L Y C H I L D H O O D

HEAD BANGING HEAD TURNING AND ROCKING

INTRODUCTION

Children often develop a series of ritual and rhythmic movements in connection with falling asleep The rituals are performed conscciously while the child is awake as a pleasant and playful preparation for the coming sleep Rhythmic head turnings or rockings can occur when the child is awake and tired but they are more commonly associated with a lower degree of wakefulness The child is approaching sleep generally in the evening but also during night waking The intensity of these movements varies from single turns of the head on the pillow to rocking movements involving the entire body and causing the bed to shake Sometimes the child s head knocks against the headboard with a bump or with other rhythmical sound effects thus eliminating the line of demarcation between jactatio capitis and head banging. Otherwise head banging is generally taken to refer to the less frequent condition in which the child, fully awake bangs its head against the floor wall or end of the bed either because it is angry or because it seeks satisfaction.

In the present essay this distinction will be retained as far as is possible Interpretation has been assisted by the mother s description of situations in which rhythmic movements occur

Little has been written on the occurrence of these conditions The few previous investigations which it has been possible to track down have been concerned with retrospective information. Lourie (6) states that 15 - 20 % of the children in an unselected child clinic population had "rocked, banged or swayed in one form or another for longer or shorter periods Mothers in a randomly selected obstetrical ward population who were interviewed by letter two years afterwards stated according to de Lissovy (5) that 15 % of their children were or had been head-bangers The response rate in this investigation was 75 %.

An account will be given here of the occurrence and course of rhythmic head bangings head turnings and rocking in a sample comprising 212 randomly selected children in the prospective longitudinal Stockholm study Co-variation with habitual thumb sucking sleep disturbances external sleep conditions outbursts of temper and bruxism in certain ages will be statistically tested.

Method

Information on these forms of behaviour has been obtained from VI: 15 and VI: 21 from 9 months to 5 years The occasional and the definitive habit have been segregated except as regards head turning These conditions have no longer been enquired after under a special heading at six years and subsequently but the few children still retaining the habit at 4 and 5 years have been followed up until the age of 8

RESULTS

Frequency

The percentage distributions of the various forms of rhythmic movement are summarized in Table 1 and fig 1 They can occur simultaneously in one and the same child or as isolated symptoms Rhythmic head or body movements occur so frequently before and at one year that in this normal child sample the behaviour is the rule rather than the exception. Since there is no sex difference boys and girls have been combined in a single group

Table 1. Head turning head banging and rocking at various ages Percentage distribution (cross-sectional)

	9 mths (n=203)	12 mths (n=207)	18 mths (n=194)	24 mths (n=204)	36 mths (n=202)	48 mths (n=204)	60 mths (n=198)
Head turning	24	24	26	14	7	2	3 5
Head banging	28	39	30	13	4	4	2
Rocking	43	27	12	10	3 5	3 5	3
Any of these rhythmic movements	66	61	45	26	12	8	6

Rhythmic body movements are generally associated with tiredness or occur as a kind of rocking to sleep. They can last from a few minutes to a matter of hours. Movements connected with settling and bedtime behaviour are often repeated identically night after night during the period in which they occur On the other hand variations between individuals present a wide range of alternative methods of obtaining gratification or relaxation. Some children lie on their stomachs beating their foreheads against the pillow while others lie on their backs and beat their pillows with the backs of their heads Again some stand on all fours rocking and knocking their heads against the end of the bed while others stand or kneel or lie with their entire body rocking with a motion that may be either gentle or violent The bumps or creaks produced by repeated impact against the walls or the ends or bottom of the bed do not appear to irritate the child: the same cannot be said of those around the child, and there are liable to be complaints from the neighbours

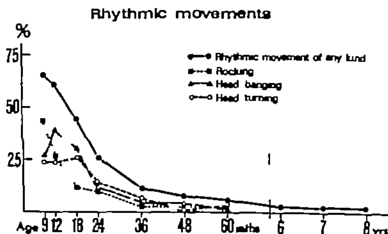


Fig 1. Incidence of rhythmic movements at various ages Percentage distribution. Cross-sectional figures

Apart from bedtime behaviour one and the same child can also indulge in head banging for other reasons during the day Some children exhibit no bedtime symptoms: instead they bang their heads exclusively during the daytime there being no apparent connection between

this rhythmic banging and any tiredness Sometimes head banging is provoked by an acute situation, when the child displays disappointment and anger or again during play or toilet training when the child is quite content and seeks amusement by banging its head against a wall a door or the side of the bath. In some cases the child displays pleasure during this behaviour or listens appreciatively to the sensation it creates in its head. The following table is the result of an attempt to elicit from mothers descriptions how many children resort to head banging in other situations besides obvious tiredness or settling down to sleep

Table 2. Head banging as an expression of anger or of happiness Percentage of total number of head-bangers at different ages

	9 mths (n= 59)	12 mths (n= 61)	18 mths (n= 58)	24 mths (n= 23)
Disappointment anger	5	11	29	26
Sensation and/or happiness	20	15	10	9

Persistence

Any of the rhythmic movements mentioned above can occur episodically (mentioned only on one or two occasions during the investigation) while in other cases they can be reported as recurring year by year up to at least 8 years On page 78 is shown the number of times children have been reported as exhibiting at least one of the symptoms The estimate is based on a pure sample i e the children were not absent on any occasion during the investigation between 9 months and 8 years

Reported on one occasion from 9 months to 8 years	44
two occasions	45
three	30
four	24
five	5
six	1
seven	1
eight	2
nine	2
ten	3

None of the children in the sample commenced its observed behaviour later than at the age of 18 months Most of the children began before they were one year old. Of the entire group only 7 began between 12 and 18 months

Six children (4 boys and 2 girls) or approximately 3 per cent of those investigated still rock rhythmically at the age of eight before falling asleep often hugging an object of some kind and humming in time to their rocking

Covariation-testing

Statistically speaking children still set in the habit of rocking at the age of three years are not more prone than others to habitual thumb sucking (X^2 - 0 111) nor are they considered particularly irascible (X^2 - 0 108) Once they have fallen asleep they do not as a rule sleep worse than other children (X^2 1 315) and they do not sleep in a separate room more often than other children (X^2 - 1.512) There is no relation to bruxism (X^2 - 0 805)

DISCUSSION

Unfortunately the children s rhythmic body movements were not systematically registered during the period preceding nine months We know from experience that this behaviour becomes more frequent during the second half of the first year of life as the child acquires more control of its muscular apparatus This is particularly true of rocking

movements performed by the child in a sitting or standing position and leaning against the edge of the bed. The frequently peak at 9 months indicated by the curve on page 76 is mainly due to rocking movements of this kind. Rhythmic head shaking and head turning do not attain their peak until 12 and 18 months respectively

Rocking is classed by certain psychoanalysts among the autoerotic infant activities of Freud s classical definition: these manifestations of sexual impulses can be recognized from the beginning but at first they are not yet directed at any outer object Each individual component of the sexual impulse works for a gain in pleasure and finds its gratification in its own body" (3) Spitz (7) has made a detailed study of rocking and other phenomena following observation of infants whose mothers were imprisoned for criminal offences In his view the condition is due to an emotionally unbalanced mother-child relationship The impulsive contradictory behaviour of the mothers precludes the development of normal object relations with the result that the child has to resort to narcissistic expressions of instinct Spitz observations refer to infants whose mothers are in prison and who lack normal contact with the outside world He finds that in 51 per cent of the 140 children at the institution rocking had been observed during infancy until 12 months The percentage incidence is not very different from that noted cross-sectionally in this normal child sample at 9 months (rocking = 44 % some kind of rhythmic activity = 67 %) Consequently it is hard to believe in the adequacy of Spitz interpretation of rocking as being due to the psycho-toxic influence of impulsively capricious mothers

The majority of rhythmic movement symptoms occur during infancy During this time the possibilities of object seeking movement are limited by the incompleteness of the neuro-muscular apparatus The majority of cases occur before the child can lift itself into all fours from a sitting or prone position or during the period when it can lift itself up given something to lean on but is uncertain of how to return to its former position Thus the first of these limitations is dictated by the level of the child s development When the child has developed a greater capacity for voluntary movement another limitation is imposed by the adults around it in the form of a high cot or

a playpen. In the event of frustration and heightened emotional tension, the motorio impulses provide a distraction and a safety valve Rocking provides a pleasurable form of relaxation when the child is tired. Different stereotypes repetitive rocking or swaying movements of the body or parts of the body can be observed in chronically ill autistic and CP children as well as the mentally retarded and blind. Rhythmic movement provides gratification and relaxation regardless of whether the obstacle to normal movement and contact with the environment is external or internal The growth obstacle disappears in normally developed children while in sick or defective children it is liable to persist In both cases habits may be formed as conditioned reflexes to particular often daily recurrent situations in the children s lives These are generally concerned with bedtime but they are sometimes solely connected with the sensation of tiredness

Escalona (2) observes the remarkable fact concerning physical autostimulation in infants that the same behaviour may sometimes have a calming effect while on other occasions or in other children it appears to cause excitement She also reflects that rocking and swaying produce the same kinds of sensations as the child often experienced in its mother s hands No doubt the use of cradles in earlier times was prompted by the realization that gentle rhythmic body movements had a calming effect Rocking has been used for centuries as a soporific and is still used today although the cradle has been abandoned owing to ambiguous assertions of its injurious consequences

It is interesting to see how the causes of head banging change with age The interpretations based on the situation described show that numerically head banging on account of anger or impotent fury undergoes a relative increase with increasing age Acute disappointment in a play situation or at bedtime become an increasingly dominant cause This behaviour too can crystallize into one of the child s typical reactions It bangs its head violently on the floor several times sometimes hurting itself in the process There is a striking resemblance here to other aggressive sel.-injurious symptoms Confined movement can of course be one of the causes of angrr To this is added the sensation of helplessness. Relaxation and gratification are sought using the means available as in the following case A girl who has

disturbed her mother in a provocative manner every day is confined in a playpen. After reacting to her predicament by screaming and crying for hours on end the first few days she begin banging her head for hours on end instead. During the intervals between head bangings she sits and imagines things The thought of captive animals in cages and their rockings bangings and subsequent resignation is never far away (1) No fixation occurred in this particular case By the time the girl was 18 months old (6 months later) the symptoms had disappeared.

Apart from expressing despair head banging though generally in a somewhat milder form can also express happiness or a new pleasing sensation. There is no question here of disappointment instead the child has encountered a new acoustic or tactile experience which it can achieve on its own and which it is continually seeking with a gratified intrigued expression. Children who sit banging against the wall or the side of the bath while waiting to defecate during their toilet training presumably have mixed feelings in their quest for gratification.

EFFECTS OF LONGLASTING JACTATIO

Two of the cases in this study where rocking and turning in connection with falling asleep remained habitual until the age of eight years exhibited symptomload above average (see Ch. XVII) This applies only to such deviations as were noticeable to the mother since the personality tests carried out at the time have not yet been analysed. Nor have the many head-banging children suffered any noticeable injury as a result of their persistent habit This is in agreement with the Kravitz s study of 135 headbangers (4) It is possible that in terms of environment and ability these children are not significantly different from children with other fixed early childhood habits Head banging during infancy is not a sign of retarded development autism or cerebral pares though these conditions are presumably more liable to produce self-gratificatory and self-injurious stereotypes

SUMMARY

A description is given of the occurrence of rhythmic movements such as head banging head turning and rocking in a longitudinally studied sample of 212 children At the age of three years 12 % of the children indulged in rhythmic movements of this kind and 6 % of them continued to do so at the age of five The stereotypes at three years exhibit no statistical connection with habitual thumbsucking night waking or bruxism, nor do children sleeping alone in a room exhibit more stereotypes than others

Headbanging occurs as a habit in connection with tiredness and settling at night and as an expression of emotional disturbance In some cases the child bangs its head to express happiness. Headbanging as a reaction to disappointment becomes relatively more frequent between the ages of 2 - 3 years

The behaviour begins mostly during infancy in a few cases between 12 - 18 months None of the children in this series began later than 18 months Six children (3 % of the 200 in the sample) continued their rhythmic rocking at bedtime without interruption until they reached school age In cases where the behaviour persists it is compared to a conditioned reflex in search of relaxation and gratification.

disturbed her mother in a provocative manner every day is confined in a playpen. After reacting to her predicament by screaming and crying for hours on end the first few days she begin banging her head for hours on end instead. During the intervals between head bangings she sits and imagines things The thought of captive animals in cages and their rockings bangings and subsequent resignation is never far away (1) No fixation occurred in this particular case By the time the girl was 18 months old (6 months later) the symptoms had disappeared.

Apart from expressing despair head banging though generally in a somewhat milder form can also express happiness or a new pleasing sensation There is no question here of disappointment instead the child has encountered a new acoustic or tactile experience which it can achieve on its own and which it is continually seeking with a gratified intrigued expression. Children who sit banging against the wall or the side of the bath while waiting to defecate during their toilet training presumably have mixed feelings in their quest for gratification.

EFFECTS OF LONGLASTING JACTATIO

Two of the cases in this study where rocking and turning in connection with falling asleep remained habitual until the age of eight years exhibited symptomload above average (see Ch. XVII) This applies only to such deviations as were noticeable to the mother since the personality tests carried out at the time have not yet been analysed. Nor have the many head-banging children suffered any noticeable injury as a result of their persistent habit This is in agreement with the Kravitz s study of 135 headbangers (4) It is possible that in terms of environment and ability these children are not significantly different from children with other fixed early childhood habits Head banging during infancy is not a sign of retarded development autism or cerebral pares though these conditions are presumably more liable to produce self-gratificatory and self-injurious stereotypes

CHAPTER XIII

EXPECTATIONS AND REALITY CONCERNING TOILET TRAINING

E X P E C T A T I O N S A N D R E A L I T Y C O N C E R N I N G T O I L E T T R A I N I N G

INTRODUCTION

The purpose of the following study of toilet training is to provide a general account of parental procedure the stage at which training begins and the final result: complete control of the bladder and bowels insofar as this materialises before the age of 8 years The essay will deal with the effects of early training of compulsion in connection with training and the relationship to certain behavioural variables in the child.

Many parents expect a great deal of toilet training and start early so as to obtain results as soon as possible The chronological relation between the commencement of training and control of the functions will be estimated for different groups of children. Continuing contact with the children has also made it possible to assess the stability of the capacity attained. The elements of compulsion occurring in toilet training have in certain quarters been ascribed considerable importance in the development of certain behavioural characteristics This will also be studied to a certain limited extent

The material also makes it possible to test the hypothesis that the individual rhythm displayed by the child at an early age (infancy) with regard to bowel function helps to determine the problems arising in connection with training (6) The regular child is supposed to be better placed to withstand the stresses of training without conflicts

The concepts of enuresis and encopresis are discussed in a later section. The differences between the primary and secondary forms are tested in different variables

COMMENCEMENT OF TRAINING

DEFINITION

The age at which the first effort is made to teach the child toilet behaviour is taken to mean the age at which special steps are introduced to adapt its evacuations to a particular time and place In order for training to be considered regular these efforts must have been made at least once a day and without any lapses.

Material and method

The material is derived from the prospective longitudinal investigation of the 212 randomly recruited children. Data from the stage of development at which training begins is in progress and concludes are always relatively recent so that there is comparatively little risk of events being remembered incorrectly The fixed form of the interview with its multiplicity of questions provides a good opportunity of endeavouring both qualitatively and quantitatively to capture the variable behaviour that precedes the full development of the function.

The variable questions on toilet training are to be found in interview form VI: items 30 - 46 In order to test differences relating to social class the median ages of children at the commencement of training in families belonging to the uppermost social class have been tested against those from the lowest social class (score 4 - 6 as against score 14 - 20 according to Graffar s modified scale) (7) Data concerning the composition of the family and the mother s education have been taken from the longitudinal social chart 1 - 3 years items 24 and 80 respectively

RESULTS

The first deliberate attempt at training in the sample is reported at 1 month, when a boy is regularly held out over a newspaper At 3 months 4 % of both boys and girls are being trained in a similar way by holding them out. At 6 months methods have begun to vary among those who have commenced training. Some are already being placed on a pot-chair and either supported by the mother or secured by straps The first lapses in training are also noted at this point. At 9 months between 40 - 50 % are sitting on a pot or pot-chair mostly the latter where the number of children secured by straps rises to attain its maximum at 12 - 18 months At 12 months the first reports are noted of use being made of the adults toilet presumably with assistance from an adult By the time they are 3 years old, over half the children have had experience of the ordinary toilet

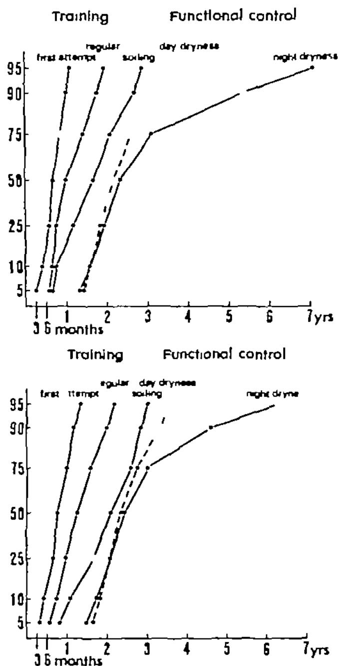


Fig 1. Cumulative percentile curves for the ages of training and functional control Plotted on normal probability paper
Upper picture refers to girls
Lower boys

Fig 1 present cumulative percentile curves for the ages at which training was first attempted and of which continuous regular training started. The median age of the first attempt (see also Table 1 page 94 for the girls is 8 4 months with a range between percentiles 5 and 95 from 3 5 to 12.7 months The corresponding median age for boys is insignificantly higher (9 months) with the first attempt for 90 % of them distributed between 4 4 months and 15 months Thus training begins for perhaps just over half the children before they can sit without a support by holding them out over a napkin a newspaper pot or toilet

In these early cases t is very common for a lapse to occur after some time has been spent trying to devise a form of training that will produce results Continuous regular training can be postponed several months by repeated lapses The median age for the girls is 10 9 months and for the boys 13 9 months for the whole sample 12.3 months A significance test of the median age differences gives p = 05 (X^2 = 4 949)

Neither the mother s education, the social status of the family nor previous experience of children bear any demonstrable relation to the commencement of training. Relatively speaking there are as many children starting training before and after 9 months in families where the mother has at least matriculated (education score 1 + 2) as in families with a lower educational standard (score 3 - 5) (X^2 = 0 192) A similar random distribution with regard to early attempts at training is also revealed by comparisons of first-born children and older siblings (X^2 = 0.012) The median ages for children from families with different social scores according to Graffar s division are given in Table 1 (page 94) The differences are negligible

DISCUSSION

Early commencement may reflect a high degree of confidence in success through early training or it may stem from a less calculating habit dictated by practical considerations A comparison of data obtained in the same way from the longitudinal parallel studies in London Paris and Stockholm has already served to show (4) that there are

considerable differences between mothers in culturally related countries The child in the London study is on average trained far earlier (median for the first attempt - 2 2 months) than the child in the present study The rather surprisingly early commencement of toilet training in London may be due to practical reasons namely the labour-saving effects of avoiding extra washing Disposable napkins are not used nearly as widely in London as in Stockholm. Consequently we are not entitled to draw any sweeping conclusions concerning the existence of different attitudes to toilet behaviour and different degrees of confidence in the efficacy of early training on the part of mothers with different habits in different societies. To the mothers in the present study however the use of disposable napkins is probably the simplest and most natural way of negotiating the problems of the first half year

The fact that regular training begins far later on average in the case of the boys is probably no more than another sign that they have greater difficulty in adjusting to training As will be shown in due course this reluctance often forces mothers to abandon training for long periods, and it is above all the boys who resist training This may be due to a difference in the maturity rates of the sexes

Ideas concerning the point at which toilet training should begin are clearly dictated by other factors than education and social background. Attitudes to toilet behaviour and disciplined training may have been established long before parenthood otherwise one might have expected different results from the more educated mothers. Yet during the last few decades there has been a considerable information campaign in the form of brochures and periodicals stressing the need for an adjustment of the pace of training to the individual stage of development It may be difficult for influence of this kind to prevail over attitudes acquired during childhood and adolescence

T H E D E V E L O P M E N T O F F U N C T I O N A L C O N T R O L O F T H E B L A D D E R

DEFINITION

Doubts are sometimes raised as to the juncture at which full control of the bladder is attained. Periods of uncertainty and relapse into wetting are frequent Temporary behavioural regressions of this kind are taken into account here as with other functions connected with growth. A long period of observation is required before one can claim that full control (= practically always dry) has been attained. The percentile values in fig 1 are based on a follow-up of the function until one year s freedom from symptoms had been established. Relapses into wetting after this period have been classified as secondary wetting and have not affected the time given for primary control. As a result of this mixture of primary and secondary cases of inability to control the bladder the cross-sectional figures derived from investigations of wetting frequencies at specific ages are on a higher level.

Method

The data of functional control are obtained from interview form VI: item 39 and 40 Only the children described by their mothers as "practically always" dry have been included in the group with complete functional control unlike those who "usually" or sometimes are dry The graduation of 24-hour wetting frequencies provided by the interview answers provides scope for a detailed assessment

RESULTS

Daytime bladder control

Given the above criteria, the median age for day dryness (cf fig 1) for girls is 26 2 months and for boys 27 9 months The difference is not statistically significant ($p = < 10$) Despite the lack of significance in this material similar results have been obtained in other investigations (1 2) and the trend has invariably been the same.

Nighttime bladder control

The juncture at which night dryness is attained has been calculated subject to the same requirements as day dryness regarding the period of observation. In the case of children who have been woken during the

night (not those who have woken of their own accord) to pass water and have consequently avoided wetting their napkins or beds the juncture at which this arrangement ceased has been noted and taken as the time limit for night dryness Brief relapses of a temporary nature in connection with illness or special circumstances have been ignored in an overall assessment that a child has been dry practically the whole time The boys are also behind the girls (median ages 28 5 and 27 6 months respectively) as regards night dryness though the difference is quite small and not significant

W H E N I S C O N T R O L A T T A I N E D O V E R T H E B O W E L S ?

Method

The answers to column 38 of the interview form VI show the point at which the child gained control of its bowels The attempted structural grading of the frequency with which the child succeeds may appear exaggerated but it serves to define the degree of control. This gives a better picture of the functional fluctuations during the development period than would be obtained from mere affirmative and negative answers.

RESULTS

Bowel control is attained by the girls in the sample at a median age of 20 months and by the boys at 25.7 months (fig 1) An X^2 test of the median ages for the sex difference is significant at a level of 0 1 %.

There are children who have been reported clean from the age of 6 months and have never subsequently at least not up to the age of eight years soiled themselves. Other children fluctuate between success and relapse or do not succeed at all - particularly in the case of boys - in attaining the steadiness covered by a year s observation until they have almost reached school age

Thanks to their own attentiveness and their observation of signs given by their children, mothers can often achieve complete success in their efforts at toilet training for periods of half a year Children with congenital or acquired regularity of evacuation do not require anything like the same amount of supervision as others But even children who have thus avoided causing inconvenience for considerable periods can suffer relapses: the younger the child, the less certain its control.

Only 17 % of the children who at 9 months were regarded as having reasonable control of their bowels were noted for the same high degree of functional ability at each subsequent observation until the age of 3 years (12 18 24 and 36 months) Thus relapses are the rule and there is little possibility of predicting the juncture

at which steady control will be attained on the basis of conditions at 9 months

More confident predictions can be made in this respect at 12 months though even at this point little more than a third of the children in control of their bowels retain steady control throughout childhood (48 % of the clean girls and 31 % of the boys)

Corresponding predictions at 18 months regarding continued cleanness up to the age of 3 years are almost 100 per cent correct in the case of the girls while as yet little over half the clean boys retain steady control of their bowels.

Children who were clean at 24 months both boys and girls exhibited the same steady capacity at 36 months

Conclusion

Clearly the functional standard attained early represents a false security Girls achieve stabilisation at upwards of 18 months boys at upwards of 24 months The incapacity for complete bowel control which some children still exhibit at 4 years or which constitutes a regression after years of control (= primary and secondary encopresis) will be dealt with later in a special section.

DATA-SUMMARY IN TABULAR FORM

The median ages for the commencement of training and the attainment of functional control are summarised in the following table

Table 1. Median ages of first attempt at toilet training onset of continuous training day dryness night dryness and bowel control.

	Median age (calendar months)				
	First attempt at toilet training	Starting continuous training	Day dryness	Night dryness	Bowel control
Total sample	8 7	12 5	27 4	28.1	23 0
♂	9	13 9	27 9	28 5	25.7
♀	8.4	10 9	26 2	27 6	20 4
Soc score at 2 yrs of age (Graffar)					
4 - 10	8 8				
11 - 13	8 9				
14 - 20	8 5				

THE RELATION BETWEEN THE DURATION OF TRAINING AND THE FUNCTIONAL CONTROL ATTAINED

A. DAYTIME BLADDER CONTROL. RESULTS

Table 2 contains a summary of the average time elapsing between the commencement of training and the achievement of steady bladder control during the daytime The division into groups according to the ages at which training began (before 9 months between 9 - 12 months and after 12 months) relates to the occasions on which the children were investigated.

Table 2 Duration between first attempt at toilet training and dryness in the day

First attempt at training	Time differences between first attempt and day dryness (mean in months)		
	♀	♂	total
at and before 9 months	23 6	21	22 3
9-12	19 5	20 1	19 8
> 12	12.9	10 5	12 5
all ages	20 2 (n=86)	20 4 (n=120)	20 3 (n=206)

The average time difference between the first attempts at training and the point at which day dryness was attained is 20 3 months in the 206 cases where both items were available (1 case of cranio-synostosis has not been included 1 case is unknown and 3 cases were lost to the investigation before attaining day dryness) The corresponding figures for girls and boys are 20 2 and 20 4 months respectively

If instead we take as our starting point the point at which regular toilet training began dividing the children into those who were trained early and those who were trained late we obtain the result shown in Table 3 Since girls generally commence regular training earlier than boys (sex difference on the significance level of 5 %, cf page 88) and become dry somewhat earlier as well the points in time regarded as early and late vary between the groups

Table 3 Onset of regular training and attainment of day dryness

	Attainment of day dryness		
♀ (n = 6)	at 24 or before	later than 24 mths	
Regular training: before 12 mths	15	28	χ^2 = 0 607
at 12 mths or later	17	26	
♂ (n = 120)	at 27 or before	later than 27 mths	
Regular training: at 15 or before	40	25	χ^2 = 0 200
later than 15 mths	30	25	

This other basis of division also fails as regards both boys and girls to produce any statistically certain difference in attainment of day dryness between children receiving late and early regular training.

DISCUSSION

If control of this function were the result of training children trained early should achieve results after more or less the same spell of training as those trained later This does not seem to apply in reality Mothers leaving the commencement of training until after 12 months spend little more than half as much time on trai-

ning before their children become dry as those commencing training before 9 months Nor is there any definite connection between early or late regular training and the juncture at which day dryness is achieved. These results are far from surprising If the prospects of success in this respect are connected with the rate and schedule of the maturing of the nervous system, the nearer the commencement of training comes to the maturity stage the briefer will be the duration of training If we assume that training has no effect either positive or negative so that neuro-muscular maturity is the sole determinant of results the median value would suggest that this maturity is first attained by girls at the age of 26 months and by boys at 28 months If this assumption is correct then clearly a great deal of unnecessary labour is devoted to a function which will develop sooner or later without any training at all Since there are hardly any mothers who passively wait for this to happen, it is impossible to obtain comparative statistics which would show whether completely untrained children tend on average to become dry at the same time as trained children.

B BOWEL CONTROL

The median age for the first attempts at training was earlier found to be c 9 months (cf fig 1) The majority of children do not achieve steady sphincter control until shortly after 2 years

To ascertain the extent to which earlier training produces more rapid, permanent results the ages at which training began have been related to the ages at which steady control was achieved as in the case of bladder control

RESULTS

Girls who began training at 9 months or earlier tend on average to attain control somewhat - but insignificantly - earlier than those who are trained late (median ages 19 9 and 20 1 months respectively)

In the case of the boys however there is a clear difference between the median ages (early trainees = 25 1 months late trainees 27 7 months median test significant at the 2 % level)

The same relations are obtained when the commencement of continuous training is used as the basis of comparison (see Table 4) This comparison also indicates the probability of a positive relation between early training of the boys and the time at which bowel control is achieved (significance level p = 05)

Table 4. Onset of regular training and attainment of steady bowel control

	Bowel control		
♀ n = 86	at 18 mths or before	later than 18 mths	
Regular training: before 12 mths	19	24	χ^2 = negligible
at 12 mths or later	14	29	
♂ n = 120	at 24 mths or before	later than 24 mths	
Regular training: at 15 or before	33	32	χ^2 = 4.770 p = 05
later than 15 mths	17	38	

DISCUSSION

The co-variation of early training and early bowel control (which is apparent in the case of the boys but no more than inferable in the case of the girls) can perhaps be explained by the fact that training is more easily and successfully applied to the less frequent and usually more regular need that characterises the bowel function. The attention given by parents to the child s indications and rhythm brings greater rewards during the training period even if the child lacks conscious control

REACTIONS TO TOILET TRAINING

As already shown an early start to training means several months of fruitless work The child is called upon to co-operate at the very stage in its growth when self-assertion and the ego are becoming factors to reckon with. There are obvious risks of serious friction and adjustment difficulties In the following section a description and analysis will be given of the interplay or conflict resulting from this particular form of contact

Method

The interview sections dealing with toilet training procedure and the difficulties encountered make it possible for the child s reactions to be differentiated into various categories (interview form VI items 30 35 36 and 37) These categories range from active resistance via passive but disgruntled submission to a more neutral or positive acceptance Mothers have not always been able to give answers placing their children in a particular group because reactions have sometimes fluctuated between different degrees of resistance in some occasions and acceptance on others Since these children are not referable to either of the main groups they have been placed in a special category ("variable in Table 5)

Children s resistance to toilet training or their display of a lack of co-operation making training appear pointless for the time being can also be illustrated by the frequency of children whose training has had to be suspended for longer or shorter periods (VI: item 30:1) In order for a *lapse* to have been noted in the interview training must previously have occurred for at least a week. Sporadic training attempts of briefer duration have not been included.

The attitude taken by mothers to the use of coercion has also been investigated, so too has their use of straps or belts either to support the child or to reduce its possibilities of escaping from the pot-chair This method has not been uniformly classified as coercive Clearly there is a difference of reaction between the child who accepts this and likes it and the child who bursts into tears and decamps taking the pot with him

The actual degree of coercion employed varies The procedure described in cases classified as coercive reflects an unflinching determination on the part of the mother often combined with threats or restrictions on the child s physical possibility of escaping from the toilet The child is replaced on the toilet repeatedly Sometimes irritation may lead to the child being held down or given a smack on the bottom. In a very few cases the child has been held on the toilet for up to 45 minutes Some cases report feeding during a prolonged procedure

Sometimes the child will accede to its parents wishes and will consent, either under protest or lured by toys to stay put Often the adults realise that the situation is untenable and adapt themselves accordingly by suspending the child s toilet training for a time

Since the age at which habitual training begins varies the estimates of frequencies and differences are based solely on the number of children who have begun their training at the age investigated. The percentages for the age of 36 months are subject to an error in that training has terminated for a number of children but the deviations are related to all the children in the sample

The other variables used in the statistical analysis to ascertain possible relations to the use of coercion concern the mother s education (form O : item 80) the mother s occupation (form O (long) items 20:1 and 2) first-born children (form O (long) item 21)

The object in using coercion is presumably to inculcate regular toilet habits as soon as possible In order to investigate the positive or negative effects of this practice on the juncture at which control is achieved, the group of children reported at one or more investigations between 12 and 36 months as having been subjected to coercion (VI: items 37:8 9) has been compared with the rest The comparison relates to the point in time at which bowel control (before or after 24 months) and day dryness (≤ 30 months) were achieved and to the occurrence of sustained incapacity or a relapse into wetting or encopresis

The group of day wetting bed-wetting and encopretic children includes all those with uncertain control at 4 years or subsequently Separate estimates have been made for primary and secondary wetters.

RESULTS AND COMMENTS

The occurrence of different reactions by the children and of measures taken by the mothers has been summarised in Table 5 and fig 2 The variables examined are resistance suspension of training, prevention of escape from the pot-chair and the use of coercion by the mother when the child refuses to co-operate

Table 5 Responses and coercive measures in toilet training
(the percentage distribution is calculated on children in training)

Age in months	Number of children in training	Active resistance or passive displeasure VI:item 35: dig 5 6	Variable VI:35:9	Neutral or with pleasure VI:35:7,8	Cessation of training VI:30:1	Tied to pot-chair VI:30:4	Coercion VI:37:8,[illegible]
9	♀ 35	17	13	70	21	41	10
	♂ 48	19	10	71	36	50	12
12	♀ 72	17 ± 4.4	15	68	29	43	24
	♂ 90	34 ± 4 9	22	43	35	51	28
18	♀ 81	20 ± 4.4	30	50	26	21	20
	♂ 103	32 ± 4 6	26	42	42	44	23
24	♀ 84	8 ± 3	8	83	14	10	21
	♂ 115	27 ± 4	19	54	22	17	24
36	♀ 85	1	7	92	0	1	12
	♂ 121	2	7	92	3	1	15

Sex diff: active resist at 12 mths of age p 02
18 p 10 χ^2 = 3 536
24 p 005
cessation at 18 " p 025
tied to pot at 18 p 001
coercion at all ages negligible differences

Girls of all ages adjust with less resistance than boys to the requirement of co-operation in training At 24 months the difference is significant on the 0 1 % level At this age more than 80 % of the girls are being trained without any problems arising while a considerable proportion of the boys are still unable or unwilling to co-operate

A special form of reaction is indicated by the data concerning retaining stools and defaecation afterwards (fig 2) In this sample only 3 two-year-old boys have been noted for retaining their faeces through fear of pain out of defiance or for other reasons It is far more common for children to defaecate immediately after the training session. Whether this is a gesture of defiance or due to a special functional incapacity it generally has a provocative effect It occurs in those apparently passively accepting training as well as in those who resist It is remarkable that one of every ten boys undergoing toilet training demonstrates his inability or unwillingness to co-operate in training in this way at the age of 18 months

Table 5 and fig 2 also show that on average the boys training has to be suspended more often than the girls The difference is probably significant (p = 025) during the observation period between 12 - 18 months The fact that no less than a quarter of the girls and nearly 40 % of the boys who had begun training by 18 months had to suspend it suggests that requirements and expectations concerning early toilet training bear little relation to the child s ability This incapacity is predominantly manifest in active resistance by the child (56 of the 64 suspensions of training that occurred between 12 and 18 months were due to resistance by the child)

The majority of mothers however show a more conciliatory and sympathetic attitude to the child resistance The different frequency curves in fig 2 often refer to the same children but with different reactions and different forms of parental action Nonetheless belief in coercion is so widespread that it was "usual at some point during the training period from 12 - 36 months for 23 % of the children in the sample If we add to these the number of children sometimes subjected to coercion in this connection, the percentage rises

COERCION AND TRAINING RESULTS

There is nothing to suggest that coercion has a favourable influence upon the intended learning effect None of the group comparisons given below suggest that coercion yields early results (Table 7) Restrictiveness in connection with training at some point during the training period has been noted to a greater extent in children who are late in achieving day dryness (≥ 30 months) or are still day wetters after 4 years The same applies to bowel control though only as regards the girls It is worth mentioning that all four of the cases of primary encopresis included in the sample were subjected to coersion during their toilet training

Table 7 Coercive measures during some period of the toilet-training in relation to early or late bladder and bowel control enuresis and encopresis Both sexes (n = 206)

				χ^2	p
Coercive measures vs	bladder control (day ≥ 30 mths)			7 765	01
	bowel	(≥ 24 mths)		2.075	n.s.
"	"		♀	5 141	025
"	"	"	♂	0 068	n.s
"	"	primary diurnal enuresis		11.497	001
"	"	nocturnal		0.859	n.s.
		secondary diurnal "		8.326	005
		nocturnal		0 029	n.s.
		encopresis (prim. + second.)		0.732	n.s.

DISCUSSION

There is no reason to suppose that mothers are less anxious to inculcate regular toilet habits early in the boys than in girls. The later commencement of continuous training in the case of the boys is probably due to more widespread and adamant resistance on their part

Girls of all ages adjust with less resistance than boys to the requirement of co-operation in training At 24 months the difference is significant on the 0 1 % level At this age more than 80 % of the girls are being trained without any problems arising while a considerable proportion of the boys are still unable or unwilling to co-operate

A special form of reaction is indicated by the data concerning re-taining stools and defecation afterwards (fig 2) In this sample only 3 two-year-old boys have been noted for retaining their faeces through fear of pain out of defiance or for other reasons It is far more common for children to defaecate immediately after the training session. Whether this is a gesture of defiance or due to a special functional incapacity it generally has a provocative effect It occurs in those apparently passively accepting training as well as in those who resist It is remarkable that one of every ten boys undergoing toilet training demonstrates his inability or unwillingness to co-operate in training in this way at the age of 18 months

Table 5 and fig 2 also show that on average the boys training has to be suspended more often than the girls The difference is probably significant (p = 025) during the observation period between 12 - 18 months The fact that no less than a quarter of the girls and nearly 40 % of the boys who had begun training by 18 months had to suspend it suggests that requirements and expectations concerning early toilet training bear little relation to the child s ability This incapacity is predominantly manifest in active resistance by the child (56 of the 64 suspensions of training that occurred between 12 and 18 months were due t resistance by the child)

The majority of mothers however show a more conciliatory and sympathetic attitude to the child s resistance The different frequency curves in fig 2 often refer to the same children but with different reactions and different forms of parental action Nonetheless belief in coercion is so widespread that it was "usual at some point during the training period from 12 - 36 months for 23 % of the children in the sample If we add to these the number of children sometimes subjected to coercion in this connection the percentage rises

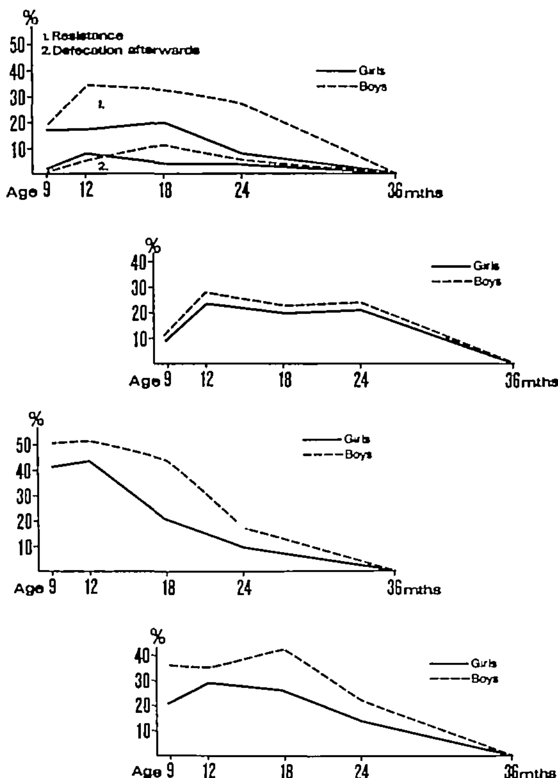


Fig 2 Incidence of coercive measures and children s responses in toilet training Percentage distribution. Cross-sectional figures

Above left = resistance and defecation afterwards

right = coercive measures

Below left = tied to pot chair

right = cessation in training

One might expect early training to increase the parents willingness to employ coercion since it remains fruitless for a relatively long period. This is not the case in the sample whether the limit for early training is put at 9 or 12 months During a certain period in training coercion is used with the same frequency in both groups As shown on page 105 it is above children who are late and unstable who provoke impatient and coercive reactions rather than those who begin their training early

Neither the mother s education her gainful employment nor her experience of earlier children produce significant differences in the use of coercion in toilet training (see Table 6) Although the frequency distribution suggest that the gainfully employed and first-time mother is less disposed to use coercion the tendency shown by the statistical analysis is within the limits of chance

Table 6 Occupational status and education of the mothers and the birth order of the children in relation to experience of coercive measures sometime between 12 - 36 months of age

	Experience of coercive measures sometime between 12-36 mths (number)	No such experience (number)	
M's occupational status when C is 1 2 and 3 yrs of age			
Full-time or part-time	11	25	X^2 = 1 617 n s
Other	72	99	
M's education when C is 3 yrs of age			
score 1 + 2	14	71	X^2 = 0 779 n s
3 + 4	15	100	
Birth order:			
First born	31	56	X^2 = 1 325 n s
Other	52	67	

COERCION AND TRAINING RESULTS

There is nothing to suggest that coercion has a favourable influence upon the intended learning effect None of the group comparisons given below suggest that coercion yields early results (Table 7) Restrictiveness in connection with training at some point during the training period has been noted to a greater extent in children who are late in achieving day dryness ($\geq$ 30 months) or are still day wetters after 4 years The same applies to bowel control though only as regards the girls It is worth mentioning that all four of the cases of primary encopresis included in the sample were subjected to coercion during their toilet training

Table 7 Coercive measures during some period of the toilet-training in relation to early or late bladder and bowel control enuresis and encopresis Both sexes (n = 206)

			χ^2	P
Coercive measures vs	bladder control	(day $\geq$ 30 mths)	7 765	01
	bowel	($\leq$ 24 mths)	2 075	n.s
		♀	5 141	025
		♂	0 068	n.s
	primary diurnal enuresis		11.497	001
	nocturnal		0 859	n.s
	secondary diurnal		8 326	005
	nocturnal		0 029	n.s
	encopresis (prim. + second.)		0 732	n.s

DISCUSSION

There is no reason to suppose that mothers are less anxious to inculcate regular toilet habits early in the boys than in girls The later commencement of continuous training in the case of the boys is probably due to more widespread and adamant resistance on their part

The interpretation of the results concerning the co-variation of coercion and sphincter instability is quite unequivocal on one point only namely that the use of coercion in toilet training does not produce quicker or more reliable results But this does not necessarily entitle us to reverse the argument and say that failures are to be seen as a prolonged defiance symptom as has been suggested concerning encopresis (1 5) A child who for a particular reason or several interrelated reasons whether environmental or constitutional lacks the resources to adapt itself promptly to the demands made by adults often provokes them to stringent counter measures The slow maturing of this sector or the rhythmic irregularity which is perhaps an idiosyncrasy of certain children and slows down the learning process can easily provoke a different kind of treatment from that experienced by children who adjust more easily and are quicker to acquire regular toilet habits

According to arguments of this kind, then delayed maturity could occur relatively independently of training In other words children who are late in achieving steady control of the sphincter are also more liable to be subjected to coercive training whether the connection involved be simultaneous or causal It is however a truism that emotional upsets can affect learning and so long as restrictive treatment of the child in toilet training cannot be shown to have any positive effect there would appear to be no good reason for resorting to such a method.

THE RELATION OF COERCIVE TRAINING TO OTHER VARIABLES

INTRODUCTION

Conflicts in toilet training are liable to have undesirable effects in other sectors A daily activity generally associated with discomfort (which is how the child s behaviour is to be interpreted) may conceivably create an attitude of defiance and resistance covering a wider sphere than toilet training alone It may influence the entire climate of upbringing and manifest itself in symptoms in a variety of sectors A test will therefore be made of the hypothesis that children who have experienced coercive training tend more than others to exhibit deviations in so-called normal behaviour The main variables considered here are refusal to eat stammering tics nail biting and defiance as interpreted by the mother

Method

The data on refusal to eat used in the statistical analysis cover the ages of 1½ and 3 years i e a considerable portion of the training period. The attitude to the food situation mainly considered to reflect emotional dependence on the mother is that expressed in the otherwise healthy child by a general aversion to liquid or solid food or both. Selective refusal of food has in this context been considered less representative of the topic under consideration. Only children noted for such a general aversion to food at one more interviews during the period in question (form Y items 73:5 7 and 9) have been included to form a group contrasting to those not rejecting food to the same extent

There were 72 children (c 35 %) whose mothers considered them to have a general aversion to food at some stage during the period 1 - 3 years The symptom varies from one investigation to another so that refusal of food is seldom persistent The greatest percentage is reported between 1½ - 2 years when 16 % of the children were noted for food problems of this kind.

Concerning speech impediments data from 3 and 4 years sufficiently close in time to the training period have been chosen to elucidate any connection with coercive toilet training Children with non-fluent (stuttering") speech occurring during their third and fourth years have regardless of the intensity of their impediment been made to form a comparison group vis á vis the others The reader is further referred to the essay on speech impediments

Coercive toilet training has been similarly tested for co-variation with nail biting or with tics. Since both nail biting and tics are rare during the period in which training is in progress these va-

riables have not been applied until the ages of 3 - 5 years Nail biting has been restricted to habitual cases (relatively few) unlike tics where all the children with involuntary tic-like symptoms during the pre-school ages have been included in the comparison group regardless of the frequency of the symptom. (Form V item 20 dig 4 - 9 and item 13 dig 7 - 9 only) The numbers of children with symptoms as defined used in the statistical comparison were as follows: nailbiting 26 and tics 68

Data from item 50 form V have been used to see whether coercively trained children are differently distributed among children considered particularly defiant between 6 - 8 years Since a 5-point scale from 0 - 4 has been used in this variable and the defiance symptom has been liable to vary in different individuals from year to year a total score for each child has been used to represent the defiance value The maximum score for the three-year period 6 - 8 years is 12 (= considered consistently defiant) and the minimum 0 (= never defiant) Only children investigated every year have been included. Some 20 % of both boys and girls have scored a sufficiently high defiance rating" (between 7 - 10) during the three-year period 6 - 8 years to qualify for inclusion in the group of defiant children.

RESULTS AND DISCUSSION

The results are summarized in Table 8 The variables given in the table are compared throughout with the variable denoting the child s experience of coercive measures in toilet training

Table 8 Coercive measures during a period of toilet training in relation to feeding troubles speech disturbances nail biting, "tics" and symptoms of defiance

Variable		Test of significance	
		χ^2	P
Refusal of food during the training period		0 334	n s
Speech impediments (stuttering) at 3 - 4 years		♂ 8 850	01
		♀ 6 224	02
Nailbiting	at 2-3 years	0 466	n.s
Tics	3-5	2.224	n.s
Defiance symptoms	6-8	0 065	n.s

The only probable connection suggested by this material concerns the variable of non-fluency in speech. Reference is made in this respect to the essay on early speech impediments (page 145), in which the observation is discussed.

It has not proved possible to demonstrate the probability of the hypotheses that training involving coercion for a certain length of time results in reactions expressing defiance (nail biting, food refusal) affective motor tension (tics) or expressions of defiance remaining after the end of the training period. The findings presented here correspond in comparable parts to those of Hetherington et al (3) who stated "neither figure (in their investigation) supports the postulated relation of severe toilet training to high degrees of obstinacy orderliness and parsimony The same negative conclusion applies to the analytic emphasis on age of toilet training" In our investigation however it has only been possible to use the mother s view of her child s behaviour to evaluate this question. The extensive material from Rorschach and other testing methods designed to illustrate the child s personality structure has not yet been studied. The question of inapparent residuary effects on personality therefor must be left open for the time being.

REGULAR BOWEL FUNCTIONING AND ITS RELATION TO TRAINING

INTRODUCTION

Thomas et al (8) have found in the longitudinal New York investigation that children whose needs (feed, defecation, sleep) are regular from the outset adjust more easily to training when it is introduced. In order to test this theory on the limited sector relating to the regularity of the bowel function, children with different rhythms during infancy have been compared with regard to training resistance at 18 and 24 months

Method

Mothers have had no difficulty in specifying whether defaecation generally occurs at the same time every day or not and they have supplied information on this point at all five investigations during infancy (VI: items 23:0 – 9) The alternative answers to the question "Is it generally at the same time or ? are distributed on a scale of never seldom, sometimes usually

Relatively few children (n = 50) have been described as regular at practically every investigation and far fewer (n = 5) have been described as very unreliable The majority in between these extremes have been classifiable into predominantly regular and mostly irregular as regards defaecation times. The dichotomy of the material based on these principles gives a majority tending towards regularity (total n = 154) but at the same time a considerable irregular group (n = 55) The number of children actively resisting toilet training at 18 and 24 months respectively has been compared in the two groups with different degrees of rhythmicity of bowel function.

RESULTS AND DISCUSSION

The wide dispersion of the number of cases in the different groups can be seen in Table 9 A chi-square test for the differences shows at 18 months a random distribution and at 24 months a probable significance of the children described as irregular during infancy being more demonstrative of their aversion to training (X^2 = 4 597 p = 05) There are no demonstrable sex differences

Table 9 Regularity in defecation during infancy in relation to resistance in the toilet-training situation at 18 and 24 months of age

Rhythmicity during infancy	At 18 months of age (numerical distribution) Active resistance variable cessation of training		Neutral or with pleasure		No information or no investigation at 18 resp 24		Total	
	♀	♂	♀	♂	♀	♂	♀	♂
Regular	29	45	36	32	6	6	71	83
Irregular	11	21	6	14	1	2	18	37
	At 24 months							
Regular	11	35	56	47	4	1	71	83
Irregular	4	21	13	15	1	1	18	37

It should be noted that changes in the regularity of defaecation are very common during the training period. Sometimes this change towards greater irregularity coincides with the commencement of training (37 cases) often it occurs later during the period for no specified reason (57 cases) The rhythm remained practically constant in 61 cases.

One can only speculate as to the cause of the unevenness thus reported. Either the mother did not succeed very well at the commencement of training in adapting her methods to the child s previous rhythm, or the child may have reached an age where attentiveness and incipient self-assertion are beginning to disturb vegetative functions In some cases regularity during infancy could make for less troublesome toilet training if the demands made of the child were postponed and made to accord with its earlier behaviour

B E D W E T T I N G D A Y W E T T I N G E N C O P R E S I S

INTRODUCTION

This section will be concerned with the frequency and interrelation of primary and secondary inability for sphincter control at different ages between 4 - 8 years The simultaneous occurrence of the different forms of functional weakness in individual children will be illustrated as will the connection between intelligence level and enuresis and encopresis

There is no standard definition of the concept of enuresis Generally the term is taken to mean involuntary wetting which in relation to the age at which it occurs constitutes a definite deviation from normal behaviour and is not connected with known organic changes. But the wealth of literature on the subject presupposes a variety of age limits. If children still in the habit of night wetting after the age of three years are to be termed enuretics c 25 % of this normal child sample would be classifiable as such, as can be seen from fig 1 page 87 It would seem to be a misuse of the term deviation to apply it to a phenomenon of such frequency A more stringent interpretation can be achieved by attaching the term to certain definite percentiles or standard deviations A working definition of this kind is appropriate as regards primary functional control Secondary enuresis which occurs after a sufficiently long period of demonstrable control is always a deviation from a normal state

The length of the observed symptom free period also affects the definition. An observer stipulating no more than about one month s sphincter control will obtain very different enuresis frequencies from the observer stipulating a year Uncertainty and temporary regressions are typical phenomena in the acquisition of growth-conditioned functions. A considerable period of observation is required in order to accommodate this uncertainty Before the control over the bladder is definitive there occurs a period of fluctuation which is obviously susceptible to influences of various kinds.

In this account of day and bed wetting information was collected on all forms of occasional, periodic or persistent inability to control the bladder Only those who lacked bladder control periodically during the year in question or at the time of the investigation are regarded as being day or bed wetters of practical importance. In those instances where incidences or calculations concerning intensity refer to wetting of a more occasional nature this is stated in the text

Encopresis is here interpreted as defined by Bellman (1) in her study of the subject namely repeated involuntary discharge of faeces in the clothes for no known organic reasons In order for such an event to be classified as encopresis it must above all have been noted in the investigation at 4 years or later up to the age of 8 years Since continual data have been collected the encopretic group has also been made to include children who have only been noted for occasional mishaps in one of the annual investigations but whose failures have been shown by a longitudinal study to be recurrent which suggests that their control of the function is uncertain.

Method

Since the formulation and gradation of the wetting variable in interview form VI items 39 and 40 at 4 and 5 is not altogether the same as at 6 7 and 8 years the contents of the digits have had to be transposed.

At 4 - 5 years item 40	digit	at 6 - 8 years	digit
never dry	0	never wetting	0
rarely	6	rarely	1
sometimes	7	sometimes	2
practically always dry		wetting several/week	3
wetting period since last visit	4	once or more/night	4
wetting occasionally since last visit	5		
always dry	9		

The following digits have been taken to correspond to one another:

at 4 - 5 years	at 6 - 8 years
0 6 corresponds to	4 3 wetting every night or several/week
4 7	2 -wetting sometimes or periodically during the past year
5	1 -now dry at night but occasionally wetting during the past year
9	0 -dry at night since the last visit

A similar transposition has been effected with respect to the day wetting variable

The longitudinal course of the symptom will be illustrated starting from conditions at four years Subsequent annual changes among these children with wetting will be related to the simultaneous background of the cross-sectional frequency of wetting in the sample A pure samples has been used in the longitudinal account i e all the children in this account have been investigated on every possible occasion.

RESULTS

Night wetting

The frequency of night wetting of all different degrees of intensity and at different ages is given in Table 10

Table 10 Incidence of wetting in the night from 4 to 8 years of age (cross-sectional percentage distribution)

	Girls				Boys			
Age in year	n	Wetting every night or often	Wetting sometimes or periodically last year	Wetting occasionally since last visit	n	Wetting every night or often	Wetting sometimes or periodically last year	Wetting occasionally since last visit
4	85	3 5	8.2	9.4	119	4 2	10 1	16 8
5	82	1 2	3 7	12.2	116	0 9	5.2	12.9
6	83	2.4	3.6	14.5	117	2.6	6	17 1
7	81	1 2	3 7	12.4	114	3 5	4 4	12 3
8	81	1.2	2.5	7.4	115	3.4	1 7	9 6

The investigation at 4 years revealed that 55 children (= 27 %) had exhibited some uncertainty in their night control of the bladder during the past observation year Many of them however had only suffered mishaps on isolated nights and can to all intents and purposes be classified together with those who are always dry at night Those with intermittent periods of night wetting during the observation period or with wetting practically every night at the time of the investigation amounted to no more than 28 (14 %) The group prone to night wetting at the very time of the 4 years investigation numbered 15 children (9 ♂ and 6 ♀ making 7 % of the sample)

Night enuresis at 4 years is mostly of a primary nature Only one of the currently or periodically night wetting four-year-olds had previously had full control of the bladder for at least one year

The decline in the frequency of night wetting in the group of children who had been current or periodical night wetters at four years or during the immediately preceding period is illustrated in fig 3

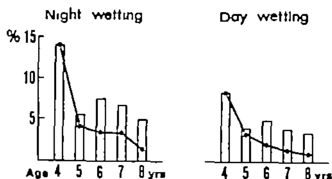


Fig 3 Cessation of night-wetting and day-wetting (= longitudinal curves) in relation to cross-sectional number (= bars) at various ages Percentage distribution.

The bars show the percentage of wetters of the same frequency degree calculated on the basis of the cross-sectional figures for the year in question. The percentage difference between the curve and the bars represents the number of secondary night wetters during these years.

The relation between primary and secondary enuretics changes from a predominance of primary enuretics at 4 years to the reverse at 8 years In comparative figures are estimated for all night wetting children, i.e including those exhibiting an occasional instability between 4 - 8 years the relation of primary to secondary night wetting is 1:2,5.

During these years night wetting is proportionally more prevalent among the boys than among the girls At 4 and 5 years the percentage ratio is 1:1,2 at 6 years 1:1,4 at 7 years 1:1 6 and at 8 years 1:1,4 Girls are very little in evidence among secondary night wetters at any frequency level A comparison of the distribution of boys and girls among those who have wet the bed occasionally or frequently during the observation period between 4 - 8 years reveals a statistical probability in favour of the boys predominans (X^2 = 4 600 p = 05)

Day wetting

The frequency of children with day wetting is given in the following table 11. It will be seen that frequent day wetting is less common than frequent bed-wetting whereas occasional instability in bladder control is noted considerably more often in the day than at night

The duration and the decline in the frequency of the symptom from 4 - 8 years can be seen from the curve in fig 3 as compared with the cross-sectional frequencies of the bars for the same ages

Table 11 Incidence of wetting in the day from 4 - 8 years of age (cross-sectional percentage distribution)

	Girls				Boys			
Age in year	n	Wetting every day or often	Wetting sometimes or periodically	Wetting occasionally since last visit	n	Wetting every day or often	Wetting sometimes or periodically	Wetting occasionally since last visit
4	85	0	9 4	25 9	119	0 8	3 3	15.1
5	82	0	3 6	23 2	116	0	3 4	18 1
6	83	0	6	19 3	117	0 8	4 3	18
7	81	1 2	4 9	16 1	114	0	2.6	7
8	81	1 2	2 5	14.8	115	0 9	2 6	4.4

Over one-third of day wetters aged between 4 - 5 years are secondary At 7 - 8 years the position is reversed with the secondary day wetters constituting two-thirds If all occasional day wetters are included the ratio of primary to secondary wetters is 1:6 for the whole of the age period 4 - 8 years

The distribution of the sexes is such that the girls tend more towards day wetting than the boys If all 4 - 8 year-old girls in the sample with occasional or persistent day wetting are compared with the corresponding category of boys the X^2 test gives a value of 4 997 (p = 05)

Encopresis

The incidence of encopresis in the material can be seen from the cross-sectional figures in Table 12.

Table 12. Incidence of soiling from 4 to 8 years of age (cross-sectional percentage distribution)

	Girls				Boys			
Age in year	n	Every day or often	Sometimes or periodically last year	Soiling occasionally since last visit	n	Every day or often	Sometimes or periodically last year	Soiling occasionally since last visit
4	85	0	0	7 1	119	0 8	4 2	9 2
5	82	0	2 4	3 6	116	0 9	0 9	5.2
6	83	0	1 2	2 4	117	1 7	1 7	6.0
7	81	1 2	0	2.5	114	0 9	3 5	4.4
8	81	0	0	2.5	115	1 7	3 5	2 6

Encopresis is generally slight amounting in the case of the children noted for occasional mishaps to little more than a slight soiling of their trousers roughly once or twice a month. The far greater intensity occuring in certain cases has also entailed not only a higher frequency but also a larger quantity of faeces in the trousers.

The ratios of primary to secondary forms are 4:1 at 4 years and 1:4.5 at 8 years This figures include all cases even those of occasionally encopresis. Three boys were reported at each annual investigation up to the age of 7 - 8 years as tending to soil their trousers. Another boy and one girl exhibited a similar persistent uncertainty of control but were symptom-free at 4 and 5 years

The duration of encopresis has been estimated against the background of conditions between 3 and 4 years and between 4 and 5 years All those habitually or occasionally exhibiting unsteady bowel control during this period have been followed up until the age of 8 years. The results are given in fig 4

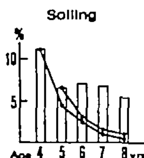


Fig 4 Cessation of soiling

The parallel curves in fig 4 denote the subsequent course of encopresis in the children noted for it at 4 and 5 years respectively regardless of whether it was primary or secondary in origin. Boys predominate on a percentage basis but the sex difference was not found to be statistically significant (χ^2 = 2.925)

Co-variation in different forms of instability of sphincter control

There is a statistically clear co-variation of day and night wetting in both boys and girls If all primary and secondary day wetters between 4 - 8 years are compared with primary and secondary night wetters the number exhibiting both weaknesses is too great to be attributed to chance (Significance level for girls p = 02 for boys p = 005) Primary day and night wetting symptoms also display some co-variation but the number of cases investigated is too small to give a probable significance

Encopresis is also commoner in the night wetting boys (χ^2 = 5 607 p = 02) and the day wetting boys (χ^2 = 7 010 p = 01) than one would expect from a random distribution. No statistical relations have been established for the girls.

DISCUSSION

Comparisons of different investigations concerning the frequency of such phenomena as night wetting day wetting or soiling are hazardous since registration methods and the length of the symptom-free interval often vary Frequency data are sometimes based on information collected several years after the event If the incidence noted in a small material such as the present comprising 200 children agrees well with large-scale epidemiological investigations of a particular defined phenomenon this also speaks in favour of the reliability of the results which are specific to the longitudinal investigation procedure

Reference can be made to two large representative Swedish investigations of 7-year-old children Hallgren s from the mid 1950s (2) and Bellman s (1), which was carried out ten years later Both employ cross-sectional figures based on a questionnaire issued to parents. In one case the investigation covered 1 992 school-starters and in the other 8 683 Hallgren reports 6 6 % and Bellman 5 8 % enuretics the corresponding figures from this longitudinal study for 7-year-olds being 6 6 %. As the frequency diminishes year by year and Bellman s figures as she emphasizes are based on children approaching their eighth birthday the three series would appear to agree well

In the study of primary enuresis carried out by the writer in 1955 (6) using longitudinal data but stipulating a shorter period of freedom from symptoms than has been adopted for the present study 4 % of the six-year-olds were found to be primary night wetters as against 4.5 % in the present investigation.

In Hallgren s study the incidence of day wetting at 7 years was 2.7 % for girls and 2.9 % for boys the former of these figures being considerably lower than the percentage (6 1 %) noted in this longitudinal study while the boys frequency is the same

As regards the incidence of encopresis comparison can be made with Bellman s comprehensive study She found on the basis of questionnaires and school medical cards an incidence of 1 5 % in children

with an average age of 7 ¾ years In the present investigation 6 children in the 7-year-old investigation and 6 in the 8-year-old investigation were registered as encopretics making 3 % of the sample at either age Bellman asserts that the frequency found by her is to be taken as a minimum. The differences may be due to the way in which information was obtained. As Bellman points out many parents are so embarrassed by soiling that they are reluctant to commit the fact of its occurrence to paper It is easier to give candid answers in a detailed interview with a psychologist one has known well for several years It should also be borne in mind that the percentages refer to a small number with the margin of uncertainty attributable to chance

The intensity of night wetting often varies even among those who are regarded as primary Weeks of nightly wetting may alternate with periods of several months during which only occasional mishaps occur Statements such as that made concerning a 5-year-old that the girl has not been dry one single night since she was born are more the exception than the rule This girl had been noted for persistent wetting at every investigation up to and including 7 years The strong element of heredity in this primary enuresis is evident from the statement that all of the mother s ten siblings had been bed wetters until between 5 and 10 years as had the mother s father and her paternal grandfather No systematic search has been made for hereditary elements in the occurrence of enuresis

Day wetting is a more occasional and varied symptom than night wetting In the case of the boys there is little chance of forecasting the course of the day wetting symptom during pre-school age A boy troubled by the symptom at 4 years runs only a slight risk of still being troubled by it when he starts school Any coincidence of the symptom with the ages of 4 and 8 years would seem to be coincidence and no more The chi-square comparison covers all forms of day wetting regardless of its frequency including the occasional wetters at 4 and 8 years. On the other hand, 8-year-old girls prone to day wetting (occasionally or frequent) include to a very great extent the same individuals who suffered from the symptom at 4 years (χ^2 test significant at a level of 1 %)

This difference is hard to explain, whether it is organic or due to the attitudes of those surrounding the child One should never lose sight of the fact that most of the day wetting occurring at these ages is an infrequent and predominantly secondary symptom. The few cases classed as primary i e unstable from an early age and with symptoms every year make little impression in a statistical comparison against the remainder of the day wetting group

Encopresis also occurs with such irregularity at these ages that one cannot possibly predict whether it will continue Of 11 children soiling themselves to a greater or lesser extent at 8 years only 4 had exhibited any symptoms whatsoever at 4 years Of the 6 reported as exhibiting relatively frequent symptoms at 8 years 4 had been found free of symptoms at the earlier age and had remained so for at least a year

COUNTERMEASURES AGAINST NIGHT WETTING DURING THE TOILET TRAINING PERIOD

The calmness with which parents await the gradual process of maturity at night stands in stark contrast to the zeal with which they endeavour to train the child during the daytime As a general rule (98 - 94 %) nothing is done to keep the child dry at 12 18 or 24 months Even if a child has still not achieved nocturnal bladder control by the age of 3 years it will as a rule be left alone (71 %) Sometimes (25 %) the child usually still half-asleep will be taken out of bed to pass water and will then go back to sleep It is very rare for children to resist the operation or to lie awake afterwards Presumably the use of napkins has reduced the eagerness of parents to get their children out of bed during the night

INSTABILITY AND INTELLIGENCE

Method

In order to see whether the different groups in the sample with primary and secondary instability differ in intelligence from one another or from the rest of the sample the differences between mean standardized test scores at the age of 5 years have been tested for significance All degrees of instability from 4 years up to 8 years have been tested against each other while again the more frequently unstable have been tested against the occasionally unstable as shown in the table below Standardized test scores (Terman-Merrill) have been used for the comparison

RESULTS

The results are summarized in table 13

Table 13 Enuresis diurna, nocturna et encopresis in relation to intelligence quotient

			T-value	Degree of freedom	Significance
Day wetting (all) versus rest of sample			150	191	n.s.
Night wetting (all)			708	191	n.s
Encopresis (all) " "			-1 168	191	n.s
Day wetting (all)	night wetting (all)		- 343	141	n s.
Primary day wetting	primary night wetting		278	31	n.s
	secondary	(all)	670	49	n.s.
night		(all)	405	62	n.s
Primary encopresis	encopresis		-1 676	11	n s
	primary day wetting		-2 217	11	p 05

DISCUSSION

No statistically significant deviations in ability can be demonstrated in the sample studied as regards the different forms of day and night wetting The only children significantly different from the

rest are the primary encopretics who are of inferior intelligence in comparison with children with primary day wetting It should be pointed out that this is a small group and its representativeness should be viewed accordingly

S U M M A R Y

The median age for the first attempt at training was 8 4 months for girls and 9 months for boys The median age for the commencement of continuous training i e the point after which there occurred no suspension of training was 10 9 months for girls and 13 8 months for boys A significance test of the difference in median age indicates statistical probability

Girls achieve daytime dryness at 26 2 months boys at 27 9 months Nocturnal dryness is achieved by the girls at a median age of 27 6 and by the boys at 28 5 months None of these differences satisfies the requirements of significance when statistically tested.

Girls are earlier in achieving control of the bowels (median age 20 months as against 25 7) The difference between the sexes is significant at the 1 % level

Children whose training began at an early age did not on average become dry during the daytime more quickly than children whose training was postponed until after 9 months Disregarding lapses of training it generally took 20 months from the commencement of training for steady results to be obtained

An analysis is made of children s reactions during the training period and of the mothers efforts to deal with them. The boys put up significantly more resistance during the period between 1 and 2 years and their training had to be suspended more often The peak is attained at 18 months when 25 % of the girls and 40 % of the boys who were being trained had to suspend it The majority of mothers took a sympathetic and exploratory attitude to the children s resistance but belief in the use of coercion is nonetheless so widespread that it was a common practice in the case of 23 % of the children in the sample during the training period between 12 - 36 months Neither the mother s education gainful employment nor experience of earlier children resulted in any significant differences in the frequency with which coercion was used.

The use of coercion in toilet training did not produce more rapid or reliable results in terms of functional control Children who who were late in achieving steady control of their sphincters ran a far greater risk than those who became dry at an early age of being subjected to coercive training

The hypothesis put forward that training including coercion for a certain period of time is reflected in other behavioural variables such as simultaneous refusal of food, tics during pre-school age or residual defiance symptoms after the end of training period has not been established as probable On the other hand the possibility of a connection between coercive training and early speech impediments cannot be discounted.

In the final section a description is given of the course and co-variation of primary and secondary forms of enuresis diurna et nocturna together with encopresis between 4 - 8 years Predictions based e g on conditions at 4 years regarding the state of the variable in question on the attainment of school age are very uncertain.

As regards intellectual test achievements using Terman-Merrill no differences in mean standardised quotients could be demonstrated between different frequency types of day and night wetting and other children. The few children with primary encopresis were of inferior intelligence to children with primary day wetting (significance 05)

REFERENCES

1 Bellman M.: Studies on encopresis Acta paediatr scand., suppl 170 1966

2 Hallgren B : Enuresis I. A study with reference to the morbidity risk and symptomatology Acta psych. et neurolog scand. 31:379 1956

- : Enuresis II A study with reference to certain physical, mental and social factors possibly associated with enuresis Acta psych. et neurol scand. 31:405 1956

3 Hetherington E.M. and Brackbill Y : Etiology and covariation of obstinacy orderliness and parsimony in young children. Child Development 34:919 1963

4 Hindley C B. et al: Some differences in infant feeding and elimination training in five European longitudinal samples J child Psychol Psychiat 6:179 1965

5 Huschka, M.: The child s response to coercive bowel training Psycho-somatic medicine 4:301 1942

6 Klackenberg G : Primary enuresis When is a child dry at night? Acta paediat 44:513 1955

7 Klackenberg G et al: The social background and its changes during the children s first three years of life Acta paediat scand. 1968 suppl 187:28

8. Thomas et al: Behavioral individuality in early childhood. New York University Press 1963

CHAPTER XLII

A PROSPECTIVE LONGITUDINAL VIEW OF EARLY SPEECH IMPEDIMENTS IN A NORMAL CHILD SAMPLE

A PROSPECTIVE LONGITUDINAL VIEW OF EARLY SPEECH IMPEDIMENTS IN A NORMAL CHILD SAMPLE

GENERAL INTRODUCTION

In spite of comprehensive and detailed studies the causes of stuttering are still unknown to us in many respects In his textbook on speech disorders in children Seeman (7) maintains that there are few pathological conditions with as many possible explanations as stuttering

During the years of childhood the impediments in children s speech presented by jerks repetition and stoppages are hard to distinguish from one another It is questionable whether this uncertainty coming as it does at a stage when the faculty of speech still lacks a sufficiently firm organization should be termed stuttering In his monography The Onset of Stuttering Wendel Johnson (5) distinguishes between non-fluency and stuttering In his view the occurrence of stammering in a child depends on the parents attitude to and evaluation of early irregularities in the child s speech. Once the suspicion has been aroused that the child is stammering the parents attitude changes. This is noticed by the child, whose uncertainty is deepened accordingly As a result of this interaction with the environment physiological irregularity of speech gives way to a self-generating rise in tension and an increasing speech disturbance which ultimately develops into stuttering But the majority of acute speech impediments are less dramatic and conspicuous in their origin Bloodstein (2) pointing to the episodic nature of early stuttering calls for longitudinal studies to elucidate the different phases.

There is no generally accepted definition of stuttering at the point where the symptom is still undeveloped. In the present account the term stuttering (stammering) insofar as it is used in stead of non-fluency in speech simply refers to a speech impediment observed by the mother and reported by her in response to the interview question: Does he (she) stammer at all? Thus the answer denotes that the child s manner

of fluent speaking has given rise to comment in some respect A working definition of this kind places certain limitations on the interpretation of the answers But great importance must always be attached to the observations which may have been made at home by the parents when dealing with such an irregular symptom as stammering particularly during its early phase The answers may also reflect an incomplete tentative but incipient mastery of the use of speech or again they may reflect an adjustment difficulty which frequently arises before a complex function becomes complete

The first part of the study will be principally concerned with the speech impediments observed in children in the sample between the ages of 3 and 8 years. The aim here will be to elucidate the prevalence of stuttering and to see whether this habit tends to persist or whether it is mostly a short-term phenomenon. Tests will also be made of certain relations to other variables which may be connected with the occurrence of stuttering The sections are headed: frequency persistence relation to accident and fright relation to speech maturity and the co-variation of speech disturbances and other behavioural variables

In the second part of the essay consideration will also be given to the incidence of retarded speech and enunciation defects in early childhood and in pre-school children.

IMPEDIMENTS IN THE FLOW OF THE SPEECH

Method

Speech impediments have been noted from the age of 3 years Data on the subject are taken from form V items 67 and 68 at 3 4 and 5 years items 46 and 47 at 6 7 and 8 years Other data used in the statistical analysis are specified in the various table headings and in the text At 6 7 and 8 years the interview question is somewhat differently phrased, namely: Has he repeated words or stammered? and Does he often get stuck on words?

FREQUENCY

Results and discussion

Table 1 shows the frequency of non-fluent speech.

Table 1 Incidence of non-fluent speech in various ages Percentage distribution. Cross-sectional figures

Age in years	Number of girls studied	Never stutter %	Occasionally %		Often %	Number of boys studied	Never stutter %	Occasionally %		Often %	Sex-difference Significance
3	85	82	14		4	121	73	22		5	p =< 20
4	85	84	15		1	116	72	20		8	p =< 10
5	81	92	6		2	115	78	17		5	p =< 02
			Seldom	Sometimes				Seldom	Sometimes		
6	83	83	10	7		117	67	15	15	3	p =< 02
7	81	80	16	4		114	60	26	12	2	p =< 005
8	81	81	11	7		115	71	17	12		p =< 10

The disturbance has been graded according to the frequency with which it occurred during the period immediately preceding the interview Frequency generally runs parallel to intensity When a child frequently demonstrates his speech disturbance it is also more conspicuous But intensity may also have undergone an acute rise in the year since the last report in children classed as occasional stutterers as were most of those affected

Boys constitute a proportionally greater percentage of those suffering from speech disturbances at each age; this is particularly the case at 5 - 7 years where the significance of the difference between the sexes is at least on the 02 level The result accords well with what has long been known concerning the greater proneness of boys to stammering (3 5)

PERSISTENCE

INTRODUCTION

The first signs of speech disturbance may predict a more conspicuous defect later on. When the children s doctor and child psychiatrist are confronted by the symptom as a subsidiary discovery during a general examination it is often overshadowed by other deviations These mild cases are seldom brought to the attention of the speech therapist since parents do not consider it necessary to consult him.

One question therefore concerns the extent to which the speech disturbances observed at 3 and 4 years respectively can presage stuttering later on. Are these disturbances a passing phenomenon? If not how likely are they to recur?

Results and discussion

Table 2 shows that the majority (60 %) of disturbances occurring for a time during the ages of 3 - 5 years do not recur at 8 years

Table 2. Number of children with recurrent speech disturbances up to 8 years of age after the onset at 3 4 and 5 years of age

First stammering		Frequence of recurrence 4	5	6	7	8 years
at 3 years	n=49x)	29	17	21	17	20
at 4		n=29	9	14	17	12
at 5			n=8	5	5	3

x) 2 of these children have since left the investigation (after 4 and 6 years respectively)

Temporary speech disturbances predominate in every annual investigation. Probably a large proportion of the many children noted for speech disturbances at 3 and 4 years are best compared to what are often termed "physiological stammerers i e their impediment can

be regarded as a stage in the development of the faculty of speech. In more than half the cases at this age the disturbance has disappeared within a year of its onset Of the disturbances beginning at 3 4 or 5 years 20 % recur only once during the observation period up to 8 years For these children the prospects are good as far as the present review extends Their disturbances have been temporary sometimes connected with specifically observed and stated situations of stress in which they have been involved.

28 children have been noted for recurrent disturbance in at least 4 annual investigations during the 6-year period. In the comparison of variables which follows below the group suffering from prolonged disturbance will be treated as a single unit The group numbered 23 boys and 5 girls The greater proneness of boys to speech disturbances is also reflected in the sex composition of this group (χ^2 = 7 248 p = 01) The difference is significant

The group is heterogeneous as regards the intensity of disturbance The common factor between its members consists in the prolonged period during which the symptom occurred from time to time or at frequent intervals The group includes some children who have consulted a special clinic for treatment of their disturbances together with others for whom a specialist examination has not been considered necessary These children will subsequently be termed the group with prolonged speech disturbance The group will be tested against the other children to see whether there are any characteristics common to the experiences or qualities of those prone to stammering which are not merely attributable to chance

THE ONSET OF STUTTERING IN RELATION TO ACCIDENT AND FRIGHT

INTRODUCTION

Sometimes when reviewing individual cases one finds statements that the disturbance began in connection with frightening stressing or exciting events. Here are a few examples of causes given for stammering in children aged between 3 - 5 years Stammered for 1 week after an accident started with an eye operation (for cataract) after a stay in hospital after he had been crying when left alone for a long time one evening at home "when she started at day care centre stammered for several months after Christmas Sometimes the reason is thought to be that the child imitates a friend. Generally the mothers are unable to think of any reason at all

The idea that dramatic events or experiences of a frightening nature tend to affect speech has been established by direct observations of this kind of immediate consequences But fright and accidents are not uncommon during early childhood, though experiences involving marked anxiety reactions are clearly distinguished from many of the apparently more trivial mishaps that can happen in the normal course of things

Method

During each visit a note has been made of whether the children in the sample have been involved in serious accidents or have been seriously frightened by anything (V: 18) It is always difficult to assess the intensity of fright but the child s emotional reactions in connection with its fright have been marked in the mother s opinion. An assessment has been made both of the immediate behavioural reaction and of after-effects and notable conditions observed subsequently

Even if the mother has not been able to observe any definite chronological link a frightening experience may possibly increase emotional tension in such a way as to increase the disposition to stammer In order to see whether such a co-variation exists all children suffering from temporary or prolonged emotional disturbances after an accident and/or a reported frightening experience of some other kind have been compared with the other 3-year-olds for the occurrence of speech disturbances Since separation from the home coupled with admission to hospital or a children home often results in emotional stress at this age children with experience of this kind at 3 years have also been included in the group Tense relationships with parents or other more elusive environmental influence have not

been included since this would hardly be feasible at the present stage of analysis of the material

The 78 children reported as non-fluent in speech at 3 - 4 years have thus been divided into three groups: group 1 (11 cases) where the disturbance has been immediately related in time to clearly specified reasons group 2 (21 cases) where the disturbance has appeared without any known relation to an accident and/or frightening experience occurring during the previous period (see below) and group 3 (46 cases) where speech disturbances have appeared without any of the above combinations

__Results__

First a few words concerning the frequency of frightening experiences noted at the ages of 3 - 4 years and their visible after-effects In one of every 7 children involved in a situation of this kind (12 of 87 children at 3 or 4 years or both ages) the mother has in her own opinion discerned unmistakeable signs of a prolongation of the emotional upset caused by the fright In the other children who have had isolated upsetting experiences the after-effects have generally been of brief duration that is to say they have not appeared in such a way that the mother has been able to observe comprehend or report them.

Five of these definitely frightening incidents were clearly related in time to the onset of stammering In five other cases the reason has been thought possibly to lie in the child s separation from the home in hospital or with strangers In one case finally the boy started stammering after corporal punishment Thus a causal connection with definite emotional tension has been found possible in a total of 11 of the 78 cases where speech disturbances first appeared at 3 or 4 years

The incidence of known frightening experiences in stutterers and non-stutterers is shown in Table 3

A comparison between groups of children with and without speech disturbances reveals a fairly even distribution of registered accidents When all the boys investigated at both 3 and 4 years are included in the X^2 test the value of X^2 is 0 038 = n.s The corresponding value for the girls is 1 365 = n.s If the stuttering children whose etiology assumed known (11 altogether) are excluded from the statistical

Table 3 Non-fluency in speech at 3 or 4 years and its relation to accidents during the corresponding observation years

	Boys number	Accidents fright	Girls number	Accidents fright
Speech disturbances first appearing at 3 or 4 years	52		26	
Probably known cause	8	4	3	1
No known cause	44	14	23	7
No speech disturbance at 3 or 4 years	66	24	54	24
Not investigated at 3 or 4 years	4	-	10	-

estimates the X^2 values are 0 240 and 1 362 respectively

Table 4 shows the results concerning a possible connection between the persistence of speech disturbances and the known circumstances attending their onset according to the group division described on page 135

Speech disturbance beginning more or less dramatically at 3 or 4 years in connection with a likely and known cause do not tend to recur more than speech disturbances beginning in a different manner Children with persistent disturbances (= disturbances noted on at least 4 investigations between 3 - 8 years) tend rather to recur more frequently in the group where no definite chronological connections have been specifiable the proportions being 2 of 11 and 23 of 67 respectively However the difference is not significant

Table 4 Number of children with recurrent and persistent speech disturbances in groups of different etiology

Onset of stuttering at 3 or 4 years		Frequency of recurrence at 5 yrs	6 yrs	7 yrs	8 yrs	Persistent stuttering group
Known incident chronologically connected with onset	n=11	3	4	4	3	2
Known incident not chronologically connected with onset	n=21	7	8	8	8	5
No known incidents at onset	n=46	16	23	22	21	19

DISCUSSION

A temporary frightening experience is probably capable of producing an acute speech disturbance if it is powerful enough but this disturbance does not last longer than stuttering due to other reasons nor can any concealed rise in tension following the fright be demonstrated in the background to speech disturbances The cases of stuttering which have occurred during the year in which the accident happened but without being related in time to the fright could equally well be due to coincidance

FON - FLUENCY IN SPEECH IN RELATION TO SPEECH MATURITY

INTRODUCTION

It is widely supposed that stammering and retarded speech are often connected in some way A greater risk is supposed to exist when the natural uncertainty of the first efforts at speech occurs at a more self-conscious age or when parents are tensely expectant regarding the course of speech development Delayed speech development and speech disturbances might also be expected to arise from a common cause in the form of a defective speech centre

Method

Speech maturity has been psychologically assessed on a 5-point scale during the investigation of the child at 3 and 5 years The assessment has included the scope of the child s vocabulary and how it is used the length and complexity of sentences and the child s ability to communicate successfully Rating 1: single words only Rating 2: elementary sentences seldom exceeding three words or a few longer utterances interspersed with jargon. Rating 3: sentences up to six and seven words Still some difficulty in making meaning clear Rating 4: simple sentences often incomplete but adequate for most practical purposes Rating 5: mature correctly worded sentences with a vocabulary ahead of the average

The mother s opinion of her child s speech is dealt with on page 150 below together with the account of enunciation defects

The following concerns the psychological assessment of speech maturity and the relationship of this maturity to disturbed speech flow

Results

The percentage distribution of the different ratings is shown in Table 5.

There is a clear difference between the sexes at 3 years with the girls developing earlier than the boys This difference has disappeared by the 5-years assessment

The relation between speech maturity and speech disturbances is shown in Table 6

Table 5 Ratings of maturity of language at 3 and 5 years of age Percentage distribution.

	Maturity of language at 3 years of age		at 5 years of age	
	♀ n=85	♂ n=117	♀ n=80	♂ n=115
Rating 1	1	3	0	0
2	17	29	8	4
3	49	50	55	57
4	24	15	34	37
5	9	3	4	3

Table 6. Speech maturity at 3 years and its relation to speech disturbances.

	Maturity of language at 3 years of age	Number	Non-fluency in speech at 3 or 4 years	Prolonged speech disturbance
♀	Ratings 1+2	15	4	1
	3+4+5	70	21	3
	(not investigated)	(5)	(1)	(1)
♂	Ratings 1+2	37	16	5
	3+4+5	80	33	16
	(not investigated)	(5)	(3)	(2)

This investigation does not corroborate the supposition that delayed speech development entails a greater risk of stammering The group noted for poor speech maturity at 3 years (psychologist s rating 1+2) does not contain significantly more cases of speech disturbance at 3 and 4 years than the group with average and good speech maturity This applies to both boys and girls (χ^2 = 0 025 and 0 respectively) Nor do the boys noted for poor speech maturity at 3 years constitute a significantly larger proportion of the prolonged stammering group than other boys In the case of the girls the number of observations is too small to justify a separate estimate Both sexes taken together gave no significance for delayed speech maturity increasing the proneness to prolonged speech disturbance symptoms

CO-VARIATION OF STUTTERING AND OTHER VARIABLES

INTRODUCTION

Although stammering is sometimes caused by established emotional factors in which anxiety plays a prominent part there is no definite explanation for most of the speech disturbances occurring in the present series In order to test the theory advanced in psychoanalytical literature that unpleasant oral sensations are capable of producing stammering children who have had weaning trouble have been compared with others with regard to stammering tendencies (V: items 57:7 8 and 58:7 8)

Other variables which may be associated with oral disturbances have also been compared with the occurrence of speech disturbances Thus deviations concerning appetite and coercion connected with refusal to eat prolonged thumb-sucking and nail-biting have been selected as test variables The children s experience of coercion during toilet training enuresis and encopresis genital play tics temper tantrums shyness and a number of social variables have also been used to elucidate possible connections

Method

The contents of the different items used in testing the variables can be summarised as follows.

Poor appetite: the group includes children noted in more than half their visits at the ages of 1 1½ 2 3 4 and 5 for what their mothers regarded as poor appetite (V: 31:6 7)

Coercion connected with refusal to eat: the countermeasures employed by mothers in the event of refusal to eat included: verbal insistence threats of punishment physical force and punishment (V: 78: 5 6 7 8) The investigation data used in this variable refer to the ages of 9 12 18 and 24 months) The use of threats punishment or coercion of any kind at any of these ages has qualified the child for inclusion in the coercion group for purposes of comparison

The prolonged thumb-sucking group includes children noted for definite habit of finger-sucking until at least the age of 5 years (see separate essay on fingersucking) The same limit applies to the nail-biting symptom (see separate essay)

The age for coercion during toilet training has been set between 1-3 years A detailed description of toilet training methods will be found in a separate essay

Stuttering tendencies in children with primary enuresis after the age of 4 years have been compared with those of children without primary enuresis. Children with day wetting (primary + secondary) between 6 – 8 years have been related in terms of speech disturbance to children of the same age not prone to day wetting The age limits for encopresis have been fixed at 6 – 8 years Children soiling themselves at these ages have been compared with those who are consistently clean.

Data on children with tic-like spasms and the simultaneous occurrence of stuttering refer to the ages of 6 – 8 years

Mothers observations concerning the boys manipulations of their genitals are so common that attention has been confined to the most frequent instances (V: 36: 2 3 4) at two of three visits between 6 – 8 years. For girls data have been obtained from V:36: 2 (all)

Real outbursts of temper tantrums between the ages of 3 – 4 years (VII: 55:9 at 3 years and VII: 54: 7 8 9 at 4 years) and particular shyness between the ages of 6 – 8 years (V: 60:2 – 4) have been related to speech disturbances in the ages concerned.

The social variables tested have comprised social class status at 3 and 4 years (O (long): 76), the mother s education when the child is 3 years old (O (long): 80) birth out of wedlock (O (long): 17) and the birth of siblings (O:63) when the child was 3 – 4 years old.

Results

The significance of differences between the variables according to a χ^2 test are summarised in Table 7

Table 7 Speech disturbances in relation to various behavioural and social variables

		Prolonged stammering	Onset of stammering at 3 and 4 yrs	Stammering at some point between 6–8 yrs
Weaning troubles	♀	n.s		
	♂	n.s		
Poor appetite (1 5 years)	♀	too few obs		
	♂	02		
Coercion on refusal to eat (9–24 months)	♀	too few obs		
	♂	n s		
Prolonged finger-sucking	♀	n.s		
	♂	n.s		
Prolonged nail...				

		Prolonged stammering	Onset of stammering at 3 and 4 yrs	Stammering at some point between 6–8 yrs
Coercion during toilet training 1–3 years	♀	n.s	02	
	♂	n.s	01	
Night wetting > 4 years (primary secondary)	♀	too few obs		
	♂	n s		
Day-wetting (at 6–8 yrs)	♀			02
	♂			n.s
Encopresis (at 6–8 yrs)	♀			n s
	♂			n.s
Genital play (6–8 yrs)	♀			05
	♂			02
Tics (6–8 yrs)	♀			02
	♂			01
Temper tantrums (3 and 4 yrs)	♀		05	
	♂		n s	
Shyness (6–8 yrs)	♀			05
	♂			n.s
Social status at 3 years (acc Graffar)	♀		n.s	
	♂		n.s	
Mother s education	♀		n.s	
	♂		n s	
Birth out of wedlock	♀ + ♂	n.s		
Birth of siblings (2–4 yrs)	♀ + ♂		n.s	

Comments

The relation of prolonged stammering to weaning troubles is attributable to chance ($X^2 = 0$) This applies equally to children weaned from the breast and those weaned from the bottle Even if the entire group temporarily affected by speech disturbances during the ages of 3–8 years is compared with the other children the X^2 value is non-significant ($X^2 = 1\ 716$) Thus it is not possible using this technique on this material to establish a probable connection between weaning troubles and stuttering according to our working definition.

Poor appetite in the boys group is accompanied by speech disturbances far more often than one would expect from a random distribution (p = 02) The girls in the stuttering prone group are too few for a comparative estimate to serve any useful purpose

Although stuttering occurs relatively more frequently in boys subjected to coercion on refusal to eat during a considerable proportion of the speech development period the difference between the groups may be of a random nature (X^2 = 2 516)

The children in the sample whose behaviour during toilet training led to coercion (examples in the report on toilet training) are more prominent than the others among those noted for speech disturbances at the ages of 3 - 4 years (p = 01 for boys and 02 for girls) The same tendency can be observed in children with prolonged speech disturbances but it lacks significance (p = 20) However this lastmentioned group of children dominated by children whose speech disturbance began long after the conclusion of their toilet training

No connection with the speech disturbances considered here can be established for the primary enuretics nor for the children who reverted to night wetting after the age of 4 years The girls with day-wetting aged between 6 - 8 years are represented among those with speech disturbances to a greater extent than the others (p = 05) The comparatively few children (n = 19) with uncertain bowel control (encopresis) between the ages of 6 - 8 years are not represented among the children in the sample with speech disturbances at this age to a greater extent than can be attributed to chance

Children with facial twitches or other forms of tic generally mild and classed as temporary were on the other hand frequently noted for speech disturbances between the ages of 6 - 8 years This applies equally to boys and girls The level of significance is high (p = 02 and 01 respectively) Since the speech disturbance is seldom described as being so extreme as to involve accessory muscular movements there is probably no question of the tics symptom having been incorrectly diagnosed.

Equally remarkable and significant is the way in which these speech disturbance symptoms occur in children both boys and girls, of between 6 - 8 years who sometimes or frequently play with their genitals Insofar as both symptoms are expressions of emotional tension this phenomenon is merely two sides of the same thing with a common causal background. Since the parental reaction to genital play has not been investigated at these ages it is impossible either to affirm or refute the speculation that uncertainty of speech is a consequence of repeated unpleasant reactions from those around the child.

Non-fluency in speech does not co-vary significantly with thumb-sucking nail-biting coercion of refusal of food shyness (boys) or temper tantrums The variables have been tested at slightly different ages as can be seen from Table 7

The social variables tested have not revealed more than a random distribution of speech disturbance cases

DISCUSSION

Of the variables which have been tested poor appetite coercion during toilet training tics and childhood genital play are significantly evident among children with speech disturbances The implications of these relations are not unequivocal Toilet training generally proceeds during the speech development period. The mothers own statements concerning coercion reflect a special attitude during this period Of course a mother using stricter methods on her child in one respect will not necessarily have the same belief in constraint in every other aspect of training but there is no denying the latent diffusion in these cases since bowel control requires daily attention and can accordingly provide a wealth of occasions for conflicts leading to emotional tension in the child

In his monography concerning the onset of stammering mentioned earlier Wendell Johnson also found that children with non-fluent speech have been subjected to a significantly higher degree of coercion during toilet training than the control children with whom he compared them. His opinion that stuttering is produced by the interaction previously described between mother and child leads him to conclude that

both speech disturbance and coercive toilet training are due to the greater expectations parents have of their children. They expect the children to be clean at an early stage just as they expect them to be early in developing perfect speech. Presumably heavy demands on the child leave their mark on both variables

This explanatory model can presumably also be made to accommodate co-variation with eating difficulties tics and masturbation. The parents perfectionist aspirations which are incompatible with the behavioural variations of early childhood generate emotional conflict reactions in the child

In my opinion coercive training is one of several causes of heightened emotional tension. Disagreements resulting in emotional conflicts are the common factor which can result in speech disturbance as well as nervous twitches refusal to eat and an increased tendency to genital play These symptoms are merely different expressions of the same emotional tension. There is nothing in the present investigation to contradict the theory put forward by Bloemel (1) that stuttering begins as a stress reaction (primary stuttering) Acute or prolonged stress of sufficient severity will disorganize speech. Further case studies may serve to show whether the physical and emotional reactions (= secondary stuttering) displayed by older children as a result of the unpleasant sensation of not being able to speak distinctly serve to maintain stuttering and develop it

E N U N C I A T I O N D E F E C T S

INTRODUCTION

A parent is daily reminded of his or her child s speech development Both stammering and incorrect enunciation are easily observable symptoms Their occurrence can often be established without the aid of any special devices or instruments They are most adequately noticeable in the home with its wealth of natural opportunities of contact and its shifting moods and emotions A certain capacity for observation and knowledge of the basic elements of development are however necessary in order to discover the mild forms

All children exhibit enunciation defects (physiological dyslalia) during a certain stage of their speech development These defects disappear at different times in different children depending on their growth. Delayed speech maturity combined among other things with enunciation difficulties may be symptomatic of late overall development with which it may run parallel It may also be isolated and principally or exclusively connected with language If one has the opportunity of following a group of children who have had difficulty in making themselves understood e g at 3 years it is often found that deficiencies in their capacity for self-expression are gradually reduced to certain special sounds instead of applying more generally to enunciation, vocabulary and sentence formation as was initially the case But apart from these enunciation deficiencies conditioned by development cross-sectional investigations e g at 4 5 or 6 years also reveal enunciation defects in other children which have never been observed previously The first of these could be classed as primary enunciation defects and the second as secondary The secondary type is probably due to other causes than delayed general development or retarded special speech development It has occurred in a child previously found to be on a level with the speech development of other children of the same age

An account of among other things speech development as measured by Brunet-Lezine s psycho-motoric development test and Terman-

Merrill's intelligence test during the first 5 years in children in this longitudinal study has previously been published by Klackenberg-Larsson and Stensson (4) The present account deals with the frequency of articulation deficiencies together with changes in these up to the age of 8 years.

The relation of this frequency to environment variables will be investigated and the complex relationships to testing or to measured intelligence quotients will also be elucidated with the aid of several years follow-up.

In an intelligence test that is based on verbal capacity to such a great extent as Terman-Merrill, enunciation defects and delayed speech maturity should have a certain influence on the achievement levels measured. Insofar as the handicap revealed by the test at 3 years is due to a specific speech retardation, the improvement that comes with increasing age should reduce its effect on the test result The extent to which this happens will be tested by comparing the mean scores at 3 and 8 years in groups of children with and without previous enunciation defects.

In connection with clinical observations tests are made of the following hypotheses concerning the relationship between retarded speech development and other variables:

(a) Speech development is more favourable in families where there is early verbal influence and linguistic stimulation than in families with no such stimuli.

(b) Children with retarded speech development are more prone than others to be temperamental and to display destructiveness, the presumed reason being desperation and anger in the face of the inability of others to understand what the child is attempting to convey by its speech.

Method

In order to arrive at a general idea of how capable the 3-year-old child was of using speech to make itself understood, above all by

those in its immediate vicinity the mothers were asked if they could understand everything their children said The question is general but functionally oriented. The difficulties cover a variety of conditions: inarticulation baby talk poor enunciation. If the function is so poor that even the child s parents cannot understand everything it says the specified articulation defects (lisping etc) are of less consequence Their specificity do not appear for suitable judgment until between 4 - 5 years

The child s speech difficulties are registered e g in interview form V: item 65 at 3 years V: 68 at 4 - 5 years and V: 47 at 6 - 8 years

At the same time as the child was tested a psychological assessment was made at 3 and 5 years respectively of enunciation and speech maturity (form 8: items 35 and 36)

Both assessments were based on a structured 5-point scale with 1 and 5 denoting the lowest and highest levels of development respectively Enunciation has been assessed in terms of the clarity and correct enunciation of the words used regardless of vocabulary and syntax

Rating 1: Mostly unintelligible
Rating 2: Difficult to understand owing to many faulty sounds or to pervading tendency to mumble
Rating 3: Most utterances can be understood but are either not very clearly spoken or are subject to three or more pervasive childish faults of enunciation
Rating 4: Generally clear One or two pervasive childish faults or occasional lapses; or a faulty system of enunciation taken over from adults involving slurred or missing consonants
Rating 5: Clear correct speech sounds throughout

Concerning the grounds for the assessment of speech maturity the reader is referred to page 138 where a description is given of its relation to stammering.

The content of ratings as regards both enunciation and speech maturity is in accordance with an internationally compiled model and based on collaboration by the study groups

As can be seen from the description of results below the distribution of children with different rating scores is such that estimates of differences are made more manageable and meaningful if they are divided into three groups (in some contexts only two)

A. Children who are hard to understand owing to considerable enunciation defects (ratings 1 and 2)
B. Children who speak indistinctly but intelligibly (rating 3)
C Children with more or less correct and well-developed articulation (ratings 4 and 5)

For purposes of analysis the children will therefore be divided into groups A, B and C (As regards the speech maturity variable the ratings will be similarly aggregated to three groups instead of five)

The standardized scores have been used in comparing the groups mean Terman-Merrill quotients

In order to ascertain any connections or co-variations between the mother s education the parents reading activity together with the children and the latter s disposition to temper tantrums and destructiveness use has been made of the following items: from social form O (longitudinal): item 80 from form VII: item 36 and items 55 and 58.

FREQUENCY SEX DIFFERENCE

Results and discussion

The children in the sample noted at the age of 5 years for indistinct speech but not generally occasioning any serious problems include a girl whose hearing was so defective that the speech function may have been affected. The simultaneous somatic investigations have not revealed any signs of anatomical change in the organs of speech in any of the children No systematic audiological or phoniatric investigation of the sample has been carried out

The mothers opinions of their children s speech development at 3 years is shown in Table 8

Table 8. The mother s opinion of the child s speech at 3 years Percentage distribution.

	♀ (n=81)	♂ (n=121)	χ^2 test (for sex difference)
a) Hard to understand	2	5	
b) Mostly intelligible	17	32	a + b versus c p = .01
c) No difficulty in understanding	81	63	

The girls can make themselves understood earlier than the boys

The assessments of enunciation at 3 and 5 years made by psychologists in connection with the testing and investigation of the child are shown in Table 9

Table 9 Ratings of enunciation at 3 and 5 years of age
Percentage distribution.

	Enunciation			
	at 3 years		at 5 years	
	♀	♂	♀	♂
Ratings	n=85	n=116	n=80	n=115
1	2	4	0	2
2	15	29	3	7
3	40	44	25	28
4	35	24	64	57
5	7	0	9	6

Sex difference at 3 yrs: enunciation ratings 1-2 vs 3-5 p = 01
at 5 yrs: enunciation ratings 1-3 vs 4-5 n s

Even according to this structured psychological assessment there is a striking difference between the sexes at 3 years significant at the 01 for enunciation defects In the significance test (X^2) rating scores 1 - 2 have been combined in one group and 3 - 5 in the other Since the same clearly defined measure of speech defects has been used at both 3 and 5 years the rising frequency of the ratings denoting better speech capacity reflect the progressive development of speech as the child grows older

The superiority shown by the girls in this sample as regards the early age at which they are able to make themselves understood and the more advanced state of their enunciation is corroborated by many other studies (see Mc Carthy 1953) In the corresponding longitudinal study in London Terence Moore has found in a comprehensive study of speech development that at 18 months though not at ages subsequently investigated (3 years 5 years and 8 years) the girls had advanced further than the boys in terms of speech maturity and vocabulary (6)

Results

The children who at 3 years showed the greatest speech retardation and were classified as hard to understand (2 girls and 6 boys) still had certain difficulties (5 out of 8) in making themselves understood at the age of 5 years One of them spoke quite correctly for its age while the others exhibited various specified consonant defects When they started school two years later infantile speech with poor enunciation and/or difficulties with particular sounds were still present in half the 8 children originally noted as speech retarded.

Fig 1 shows the development of these considerably speech-retarded children (group a in Table 8 page 150) and the relatively inarticulate children (group b) during the pre-school years with regard to enunciation defects Although the percentage frequencies are different among boys and girls the shape of the curves is similar and the children have therefore been combined in a single group The continuous curve thus represents the diminishing trend of the frequency for the entire sample The difference between the curve and the cross-section values represented by the bars denotes the number of additional enunciation defects existing in the children in the sample at different ages



Fig 1. Frequency of children with speech retardation and enunciation defects Percentage distribution. Curve = longitudinal values Bars = cross-sectional frequency

THE CO-VARIATION OF SPEECH RETARDATION AND BEHAVIOURAL VARIABLES

Results

Children with moderately and severely retarded speech development at 3 years do not differ significantly from the other children in the sample as regards certain motoric skills (walking without support at or after 12 months) (X^2 = 0 372)

Nor can any difference be established as regards the frequency of temper tantrums at 3 years (X^2 = 0 025)

Children with retarded speech development are relatively more prevalent among those reported as being more destructive than others but the X^2 value is not significant (X^2 = 2 531) Similarly it is relatively more common for speech retardation to be found in children with less well-educated mothers but this distribution too may be coincidental (X^2 = 2 238)

If children from families with different reading habits (= reading aloud to the children) are compared with one another against the background of the speech retardation variable the following emerges Of 59 children with speech retardation at 3 years only 23 were reported by their mothers at the 2-year investigation to have had experience of habitual reading (information is lacking for 2 children) The corresponding figures for children whose mothers had not observed any notable speech retardation were 79 out of 137 (X^2 = 4 755 p = 05) Children who from an early stage had listened to this kind of entertainment and obtained more extensive language practice through being read to also occurred less frequently in the speech-retarded group

CO-VARIATION OF ENUNCIATION DEFECTS AND THUMB-SUCKING

A previous study of habitual thumb-sucking (page 50) established a statistical connection (p = 025) between prolonged thumb-sucking and lisping between the ages of 4 - 5 years This connection becomes more apparent if enunciation defects are taken to include other consonant difficulties as well as those concerning fricatives (X^2 = 7 644 p = 01) A summary of the frequencies in the fourfold table is given

in Table 10

Table 10 Consonant enunciation defects and prolonged thumb-sucking

	Consonant enunciation defects at 4-5 years (n=40)	No such defects (n=164)
Prolonged thumb-sucking	20	45
Others	20	119

DISCUSSION

The speech of many children is clearly incomplete at 3 years Even when they start school about one-quarter of those classed as retarded at 3 years still pronounce certain sounds incorrectly These enunciation defects are not serious but they are relatively persistent The most frequent deviation is an incorrect enunciation of fricatives Since the frequencies quoted for the ages of 6 - 8 years are based on the mothers opinions they presumably represent a minimum.

It is worth pointing out in this connection that parents who are in the habit of reading aloud to their children during the speech development period have relatively fewer children with retarded speech. This suggests that daily listening practice with a wider range of language provides the training and stimulus needed for adequate speech. This method of reading aloud to prepare speech development is probably the simplest most natural and from the children s point of view the most enjoyable way of rapidly achieving correct speech. The stimulus is probably of great value regardless of the hereditary element by which speech development is also influenced.

The supposition that children who cannot make themselves properly understood are more prone to temper tantrums or destructiveness than others at this early age (3 years) is not verified by this material Of course this is not to say that the observation is groundless Temper tantrums are among children of this age only too common a way of

in terms of pronunciation. The most advanced children still retain a considerable lead at 8 years

DISCUSSION

The differences in Terman-Merrill quotients between the groups at 3 years are not surprising as regards either enunciation or speech maturity Regardless of whether speech imperfections are an expression of low general ability or a specific speech retardation, the construction of the test leads one to expect these differences Tests of a child with an impaired speech function should always be supplemented by a non-linguistic test But the slight equalization that has occurred between the groups by 8 years suggests either that the element of children of low general ability is particularly dominant among 3-year-olds with enunciation defects or that the consequences of the language handicap are slow to disappear At all events, these children who are speech-retarded at 3 years run the risk of starting school with an obvious handicap and with less chance of assimilating the instruction they receive Insofar as language training combined with other intellectual and emotional stimuli is successful this particular risk group should be given priority for early admission to nursery school

SUMMARY

The speech of a randomly recruited sample originally numbering 212 children studied longitudinally up to the age of 8 years has been investigated as regards disturbances in speech flow and enunciation defects

I. The first of these are more common even in their milder and more temporary forms in boys than in girls The sex difference between the cross-sectional frequencies is clearly statistically significant between 5 - 7 years Stammering" in pre-school children is often of a clearly episodic character Temporary disturbances predominate at each annual investigation. 20 % of the disturbances first appearing at 3 4 or 5 years reappear only once during the observation period up to 8 years Many of the speech defects reported by mothers below 3 and 4 years are presumably due to speech not yet having attained sufficient stability and firmness of organization so that it is relatively easily disturbed by environmental influences during the development phase

A definite chronological connection with accidents or other defined frightening experiences was found in 11 of the 66 cases exhibiting non-fluency in speech between 3 - 5 years Apart from these presumably causal connections significance testing did not establish any tendency to stammering on the part of others who had been involved in accidents or other frightening experiences Speech disturbances appearing in connection with a dramatic experience were neither more nor less persistent than those which began less conspicuously

Significant co-variation was established with the variable coercion during toilet training which the author is disposed to interpret as an indication of a speech defect generated by conflict tension. Speech reactions were also accompanied to statistically significant extent by poor appetite tics and masturbation all of which were interpreted as simultaneous reactions in different behavioural variables to emotional tension. No connection could be established with weaning troubles thumb-sucking nail-biting sleep disturbances night wetting or encopresis shyness or temper tantrums nor with social class status the mother's education or marital status (at the

time of the child s birth), nor with the birth of a sibling.

II Enunciation defects occur as a sign of retarded speech or general development or are acquired without having been noticed previously At 3 years 2 4 % of the girls and 5 % of the boys speak in a way which even close relatives have difficulty in understanding Enunciation and speech maturity assessed by a psychologist at 3 and 5 years on the basis of a 5-point scale reveal a significant (p = 01) sex difference at 3 years but not at 5 years

A description is given of the persistence of enunciation defects up to the age of 8 years Half the children who were most retarded (unintelligible) at 3 years were still speaking in an infantile manner when they started school with indistinct enunciation and/or difficulties with particular sounds the commonest defect being lisping

Speech retardation was less prevalent in children whose parents were in the habit of reading aloud to them. This test referred to reading aloud noted at 2 years and speech retardation at 3 years. Significance p = 05

The following emerged concerning the connection between ability and speech retardation/enunciation defects The significant (p = 001) mean differences which understandably enough were established between children with different degrees of speech retardation and others at 3 years were practically unchanged at 8 years. Standardized Terman-Merrill quotients were used at both ages Although there are children with so-called specific speech retardation whose measured test results improved considerably between 3 and 8 years taken as a group 3-year-old children with speech disturbances are worse off than their classmates when they start school There is a large element of general retardation The speech-retarded infant should be regarded as a child at risk and should be given priority for development-stimulation in nursery

REFERENCES

1 Bloemel C S : Concepts of stammering The Journal of Speech and Hearing disorders 25:24 1960

2. Bloodstein O : Development of stutterers Journal of Speech and Hearing disorders 25:1:219 1960 and 25:1:266 1960

3 Johnson W : The onset of stuttering University of Minnesota Press Minneapolis 1959

4. Klackenberg-Larsson I. and Stensson J : The development of children in a Swedish Urban Community A prospective longitudinal study IV: Data on Mental Development during the first five years Acta paed. scand. Suppl. 187 1968

5. Mc Carty S : Some possible explanations of sex differences in language development and disorders Journal of Psychology 35:155 1953

6 Moore Terence: Language and intelligence: A Longitudinal study of the first eight years Human Development 10:88 1967

7 Seeman, U : Talrubbningar hos barn. Svensk bearbetning C.E. Fritzes Bokförlag 1968

time of the child s birth), nor with the birth of a sibling.

I. Enunciation defects occur as a sign of retarded speech or general development or are acquired without having been noticed previously At 3 years 2.4 % of the girls and 5 % of the boys speak in a way which even close relatives have difficulty in understanding Enunciation and speech maturity assessed by a psychologist at 3 and 5 years on the basis of a 5-point scale reveal a significant (p = 01) sex difference at 3 years but not at 5 years

A description is given of the persistence of enunciation defects up to the age of 8 years Half the children who were most retarded (unintelligible) at 3 years were still speaking in an infantile manner when they started school with indistinct enunciation and/or difficulties with particular sounds the commonest defect being lisping

Speech retardation was less prevalent in children whose parents were in the habit of reading aloud to them. This test referred to reading aloud noted at 2 years and speech retardation at 3 years. Significance p = 05

The following emerged concerning the connection between ability and speech retardation/enunciation defects The significant (p = 001) mean differences which, understandably enough, were established between children with different degrees of speech retardation and others at 3 years were practically unchanged at 8 years Standardized Terman-Merrill quotients were used at both ages Although there are children with so-called specific speech retardation whose measured test results improved considerably between 3 and 8 years taken as a group 3-year-old children with speech disturbances are worse off than their classmates when they start school There is a large element of general retardation. The speech-retarded infant should be regarded as a child at risk and should be given priority for development-stimulation in nursery school.

CHAPTER XIV

FURTHER STUDIES OF SLEEP BEHAVIOUR IN A LONGITUDINALLY FOLLOWED UP SAMPLE

(principal ages for this section 4-8 years)

FURTHER STUDIES OF SLEEP BEHAVIOUR IN A LONGITUDINALLY FOLLOWED UP SAMPLE
(principal ages for this section 4 - 8 years)

INTRODUCTION

Interest in sleep research during the past decade has been primarily of a neuro-physiological nature Refined methods have made it possible to chart the different stages of ordinary sleep Remarkable results have also been obtained concerning sleep disturbances such as somnambulism (2 5) The connection between somnambulism and dream sleep has been disproved by the appearance of the EEG (3 4 8)

The present study is not concerned with the physiological basis of sleep but rather with the way in which that basis is expressed through habits and sleep disturbances Sleep conditions have been observed and reported by the mother It is her experience of events at home during the night that is presented here The report consists of facts concerning sleeping times and sleep disturbances provided by her In many respects the present report is a sequel to the account already given of sleep behaviour up to the age of 3 years. (6) The material has been taken from the same prospective longitudinal study

An account of the wealth of data concerning sleeping habits will be divided up under the following heads: sleeping habits and length of sleep resistance at bedtime night waking and somnambulism. Our main concern will be with conditions between 4 - 8 years though previously published data may also be added to illustrate a tendency in a continuous process Data from the first year of life which have not been published before may also be included in the account because of their relevance to subsequent ages

Method

Data concerning sleep conditions are given at 4 - 5 years in form VI: items 47 - 48 and 6 - 8 years in questionnaire V: items 16 - 23 and form V: items 66 - 69 (sleeping times) At 4 and 5 years the mothers were interviewed by the psychologist following a standardized schedule of questions.A somewhat different questionnaire was

used at 6 - 8 years: this was completed at home and then supplemented during the visit to the clinic While the questions in the two questionnaires cover very much the same ground they are somewhat differently phrased. Another difference is that whereas personal interviews were a regular practice at the earlier ages they were reduced to a supplementary role later on.

SLEEPING HABITS AND DURATION OF SLEEP RESULTS

Bed time, awaking time and lenght of sleep

During the period under consideration, bedtime becomes progressively later and the number of hours the child sleeps every twenty-four hours gradually decreases. Up to 3 years of age the average sleeping time was reduced above all by the decrease and ultimate disappearance of daytime sleeping the duration of night sleep remaining relatively unaltered. As in the previous study data on sleeping and waking times to the nearest half hour were collected at every visit up to and including 8 years The times specified refer to typical weekday mornings and evenings

No significant differences have emerged between the girls sleeping times and the boys The entire sample has therefore been grouped together in each of the cumulative percentage curves denoting sleeping and waking times at 4 and 7 years (fig 1) These ages have been chosen to represent preschool and early school age Half the 4-year-olds are accustomed to going to bed later than 7 15 p.m. while half the 7-year-olds regularly go to bed after about 8 15 p.m. Differences in the duration of morning sleep tend to cancel out taking the group as a whole

The duration of sleep in an ordinary twenty-four hour period has been calculated on the bases of the sleeping and waking times reported. Some children still have a short sleep during the day at 5 years more specifically 5 % of the sample (= 10 children) as against 13 % at 4 years Three of these children sleep for anything up to 2 hours during the day As in previous investigations hours of sleep during the day and during the night have been added together Means and standard deviations for the entire period from ½ year to 8 years are shown in the graph in fig 2. After 6 years hours of night sleep are the same as hours of sleep per twenty-four

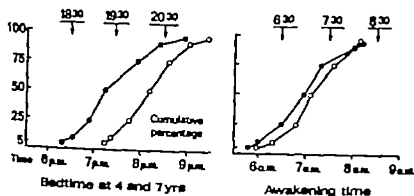


Fig 1 Sleeping and waking times for children at 4 and 7 years respectively

hours. Table 1 shows the numerical values and standard variations of the total duration of sleep per twenty-four hours on which fig 2 is based.

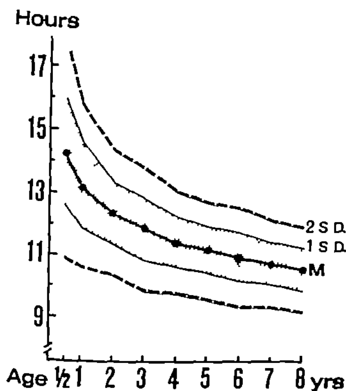


Fig 2. Means and standard deviations for duration of sleep in hours at the ages of ½ - 8 years inclusive

Table 1 Duration of sleep at different ages (means and standard deviations)

Age in years	1	2	3	4	5	6	7	8
Total length of sleep (night + day)								
Means of hours	12 3	12.4	11 9	11 8	11 6	11 1	10 8	10
S D	± 1 3	± 1.0	± 1 0	± 0 8	± 0 8	± 0 8	± 0 7	± 0

Duration of sleep and season

The correlation of duration of sleep and season i e the number of hours of sunlight per day on the child s birthday has been calculated using the Pearson correlation. Children born during the darker half of the year did not sleep longer at the time of their birthdays than children born during other seasons The correlation coefficient are shown in Table 2.

Table 2 Relation of duration of sleep to season (4 - 8 years of age)

Age in years	4	5	6	7	8
Correlation-coefficients	± 0	- 09	13	- 03	07

The correlations are weak and not significant The same applies to relations to duration of night sleep for which special correlation estimates were made at 4 and 5 years (coefficients - 01 and - 10 respectively)

Correlation between durations of sleep of different ages

Correlations of the same child s duration of sleep in different years yield the correlation coefficients summarized in Table 3 The correlations are far from high, but are at least far better than the relations calculated earlier for ages below 3 years (6)

Table 3 Correlation coefficients of duration of sleep at different ages (Pearson-correlation)

Age (in years)	5	6	7	8
4	32xxx	35xxx	(13)	28xxx
5		34xxx	35xxx	38xxx
6			50xxx	40xxx
7				47xxx

xxx = p 001

Brackets signifies correlation not significantly differing from 0

Sleeping place

The sleeping accommodation provided for a child is very largely dictated by social reality There is often a shortage of space so that many families are unable to give their child or children a separate bedroom for the first few years After a few years when the family has acquired more living space (7) a new child is often added to the family so that even if the parents now have a room of their own, the children generally have to share This process is illustrated in Table 4 by cross-sectional figures for different ages up to 8 years.

Table 4 Sleeping place Percentage distribution

	Age in months 1	6	in years 1	2	3	4	5	6	7	8 yr
Child sleeps alone	14	12	13 5	9	12	9	12	13	16	13
Child shares bedroom										
with sibs	3	10 5	17	25	35	46	54	55	59	64
with parents	70	63	58	55	42	33	22	32	25	23
other combinations	12	14 5	11	12	11	11	12			

Although practically every child has a bed of its own to sleep in many of them spend a greater or smaller part of the night in one of their parents beds generally the mother s Table 5 gives data showing developments in the sample in cross-sectional figures from 4 to 8 years inclusive The terms often and sometimes used in the questionnaire completed by the mother at 6 - 8 years have been taken to correspond to the more exact specifications of 3 - 6 times/wk" and 1 - 2 times/wk" on which the figures for 4 and 5 years are based

Table 5 Frequency of children sleeping part of the night in the bed of the parents at 4 to 8 years of age Percentage distribution.

	At 4 yrs of age (n=204)	5 yrs (n=198)	6 yrs (n=188)	7 yrs (n=185)	8 yrs (n=189)
1 Every night	18	14	7	6	6
2 3-6/week = often	12	8	15	9	6
3 1-2/week = sometimes"	8	11	14	14	6
1 + 2 + 3	38	33	36	29	18 %

The father s bed is not chosen nearly as often as the object of the children s nocturnal visits though it figures in one of every four visits by the boys and one of every six by the girls and still less frequently after 8 years Figures are only available for ages after 6 years

Adding together the numbers of children who sometimes often or always visit one of their parents beds we find as can be seen from the bottom line of Table 5 that at 6 years they comprise one-third and at 8 years barely one-fifth of the sample

Table 6 Frequency of "night-visitors in parents beds in relation to social groups and gainful employment of the mothers

At 4 years of age (n=204)		to parents bed	no visit or seldom	difference
Swedish social group	1.	13	19	
	2	23	61	χ^2 = 6 188 (2 df)
	3	40	48	p = 05
at 8 years of age (n= 193)	1	6	25	
	2.	10	72	χ^2 = 3 685 (2 df)
	3	18	58	p = n.s.
at 4 years of age:				
M. gainfully employed		23	30	χ^2 = 1 188 (1 df)
no such work		53	98	n.s
at 8 years o_ age:				
M.gainfully employed		12	50	
no such work		22	105	χ^2 = negligible

Table 6 shows the number of children in the habit of visiting their parents beds divided according to social class and the mother s gainful employment The Swedish triple classification of social status on an occupational basis has been used here Gainfully employed mothers have been taken to include both full-time and part-time employed. All three levels of frequency of night visiting shown in Table 6 have been included. Since the difference in behaviour between boys and girls is negligible both sexes have been combined in a single table

RESISTANCE AT BEDTIME

40 - 50 % of the children are reported to a greater or lesser degree as being troublesome and unwilling to go to bed when it is time for sleep This applies throughout infancy and has not diminished during the first year at school. Data for Table 7 have been taken from form VI: item 55:8 9 at 4 and 5 years and questionnaire V: item 16:2 - 4 at 6 - 8 years There is no difference between the sexes

Table 7 Children with resistance at bedtime Percentage frequency in cross-sectional sample at 4 5, 6 7 and 8 years of age

	Usually + sometimes
4 yrs	42
5	43
6	40
7	44
8	45

This unwillingness to go to bed is often a characteristic trait which constantly recurs in the investigations of certain children year after year The frequency with which this occurs is shown in fig 3 where the curve denotes longitudinal behaviour The bars give for purposes of comparison the cross-sectional percentages for the corresponding years

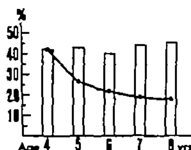


Fig 3 Persistence of resistent behaviour at bedtime

——— = longitudinal percentage curve pure sample

☐ = cross-sectional percentage

DISCUSSION

Obviously going to bed is not quite the attraction to many children that their parents would like it to be and presumably find it themselves. If this conflict is reiterated night after night widespread irritation results. Often such conflicts can be symptomatic of a more comprehensive and thoroughly strained parent-child relationship. The bare figures provide no indication of this. The percentages include both habitual behaviour (termed "usually" or often by the mother) and the less frequently recurring troubles reflected by the term sometimes" At 4 and 5 years approximately half of those putting up resistance do so habitually. This category gradually diminishes as the years pass: at 6 years c 1/3 and at 7 and 8 years c 1/4 of all those noted for difficulties at bedtime. The data analysed here do not reveal how often the parents expectations in this situation are anachronistically high nor how often the child s resistance is exceptionally easily provoked

NIGHT WAKING

Introduction

A high frequency of night waking was demonstrated in the study of sleep behaviour up to the age of 3 years (6) Here we shall examine the development of this situation up to the age of 8 years Cross-sectional figures will be presented for different ages together with subsequent developments in children with manifest sleep disturbances at 4 and 5 years

Definition

Children who have woken up during the night *after* their parents have gone to bed have been registered for night waking This is an operational definition which takes into account the possible effect of night waking on family relations rather than the point in time at which the disturbance occurs Thus a child waking up at 11 p.m. is generally more of a disturbance to a family accustomed to going to bed early than to parents who are still up Similarly early waking in the morning between 5 - 6 a.m. may be perfectly suited to the routine of one family while another may find it irritating and tiring

Method

Night waking was registered in slightly different ways at the interviews during the first five years and in the questionnaire filled up by the mother at home and completed at the clinics at 6 - 8 years of age The first of these gave a more exact description of the frequency and character of night waking and the nature of the countermeasures taken (form VI: 61 - 72) The degrees of frequency were: waking once or several times during the night 3 - 6 nights per week 1 - 2 nights per week less than one night per week and never In the questionnaire completed by the mother (and supplemented at the clinic) the incidence of night waking was graded as follows: always often sometimes seldom and never (V: 21) This difference should be borne in mind when considering the results

FREQUENCY RESULTS

There are no significant differences as regards night waking between boys and girls Both sexes have therefore been combined in a single group for accounting purposes Table 8 shows the percentage distribution of night waking between different frequency levels

Table 8 Incidence of night waking at 4 to 8 years of age Percentage distribution. Both sexes

Age in years	Nightly	3-6/week	1-2/week	all together
4 (n=204)	23	11	10	44
5 (n=198)	20	10	13	43
	always	often	sometimes	
6 (n=200)	4	10	29	43
7 (n=194)	5	8	23	36
8 (n=196)	4	5	23	32

PERSISTENCE

The cross-sectional figures illustrate the situation in the sample as a whole at different ages but they do not reflect the changes in the behaviour of the same children from year to year Nor do they show how persistent a behaviour is This is done in fig 4 starting with night waking at the age of 4 years

Method

Only children who have attended every investigation (pure sample) are included in the curves which cover disturbances of all three levels of intensity (nightly 3-6/w = often 1-2/w = sometimes) Any variation in behaviour between these three levels over the years has been disregarded. If on the other hand a lower waking frequency than the above has been reported at any of the annual investigations sleeping behaviour has been regarded as normal and

the disturbance as no longer occurring in which case any subsequent disturbance has been counted as episodic and temporary

RESULTS

Thus the curve in fig 4 refers to the percentage of night awakenings that have persisted year after year starting with the figures at 4 years The bars denote the percentage with sleep disturbances (cross-sectional data) in the pure sample at the different ages The percentage differences comprise night wakenings which are either new or have revived after having been in abeyance for a period of time

The curve suggest that nearly a quarter of night-waking 4-year-olds are liable to remain so year after year until at least the age of 8 Similarly one can see that one-third of the families with children waking at the latter age have had long experience of this behaviour

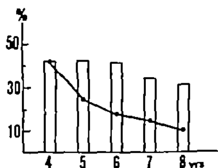


Fig 4 Persistence of night awakening in pure sample
Percentage distribution.

Curve - persistent night awakening
Bars - all night awakenings at respective ages

NIGHT WAKING BEHAVIOUR

The way in which the child behaves when it wakes up during the night can provide an indication of why it wakes up The description given of its condition by the mother has been based on a structured interview Data on the subject are included in the interviews up to and including 5 years (VI: 62: 0-9) In Table 9 an attempt has been made to group the reasons according to the mother s description. The analysis comprises children who have slept badly for a period of more than 6 months between the ages of 3 and 4 years and between 4 and 5 years The percentages are based on the total number of children in the sample

Table 9 Behaviour at awakening in the night at 4 and 5 years of age Percentage distribution, calculated on the whole sample

	At 4 yrs of age (n=204)	at 5 yrs of age (n=198)
Cheerful, just wants attention	20	18
Toilet need	12	11
Upset, frightened	4	3
Miscellaneous	4	3
(Good sleepers)	(60)	(65)

It may be mentioned for the sake of comparison that another 5 % of the children in the sample are noted at 4 years waking up frightened or upset but this has happened only on isolated occasions during the past year to children who are otherwise classified as sound sleepers The corresponding figure at 5 years is 8 %.

Concerning this topic see under headings of discussion page 177

THE CO-VARIATION OF NIGHT WAKING WITH CERTAIN ENVIRONMENTAL VARIABLES AND SPEECH IMPEDIMENTS

The environmental variables tested are (1) the mother s gainful employment (2) the child s separation from the home in a completely strange environment and (3) the child s experience of and reaction to accidents or frightening events

Method

The category of gainfully employed mothers has been made to include all those with some kind of employment at the time of the investigation no matter how regular or irregular Most of those included in the group are regularly employed on a full-time or part-time basis The comparison does not take into account where the child spends its time or who takes care of it while the mother is at work.

Variable no 2 includes the children who are cared for outside the home and by some other person than their mother or a relative not only during the day but also at night These children have been living in another private home in hospital or at a children s home

Variable no 3 comprises children who have been involved in accidents or undergone some other frightening experience

In variables no. 2 and 3 the comparisons have been limited to 4 and 5 years The X^2 analysis regarding the mother s employment extends as far as 8 years.

The prolonged speech impediment variable (tendency to stammer) comprises children who were constantly noted for stammering to a greater or lesser degree between 3 - 8 years

RESULTS

The results are given in Tables 10 and 11

Table 10 Covariation of night waking and certain environmental variables.

	At 4 years	5 years	6 years	7 years	8 years
Mother s gainful employment	05	n.s	n s.	n.s	n.
Child s separation from the mother	10	02			
Accident fright	n.	n.s			

Of the variables tested it is above all the placing of the child in a strange environment that shows a significant co-variation with night waking (2 % level at 5 years) A similar tendency is noticeable at 4 years but is not significant (χ^2 = 3 026) The occurrence of sleep disturbances was also probably significantly more frequent for children with gainfully employed mothers at 4 years of age but the covariation did not appeared of any other age

Comparing the children in the group for prolonged sleep disturbance with other children with regard to stammering tendencies yields the following distribution.

Table 11 Persistent sleep disturbances vs prolonged speech impediments.

	Bad sleepers 4-6 years	Others	
Prolonged speech impediment	9	19	χ^2 = 4 524
Others	27	145	p = 05

The distribution in the fourfold table shows that prolonged night waking is combined with persistent speech impediments more often than can be attributed by chance

DISCUSSION

The supposition that children habitually waking during the night at 4 – 5 years mostly show signs of fright is not borne out by the the facts. Nightmares or a fear of the dark that upsets the child are in a minority compared to other causes It is common for children of this age to wake up because they need to go to the toilet but in most cases the reasons are impossible to trace: they wake up merely displaying a need for playful attention. Waking may be connected with physiological variations in the depth of sleep which are

a part of normal sleep behaviour Children at a superficial stage of sleep can probably be woken by such slight disturbances that it is impossible to point to any particular causes The disturbances in question may not a ways be such palpable things as external stimuli physical discomfort or needs or signs of mental imbalance In most cases it is probably sufficient to speak in terms of night waking instead of sleep disturbances if the latter are taken to refer to pathological conditions There are a few more observations which can well be accommodated in such an interpretation. Night waking often recurs persistently month after month. It may be connected with the physiological type of sleep with which the child is equipped The large group of children with night disturbances wake up without being emotionally disturbed contrary to what one would expect if waking were due to mental disturbance

These reflections are not designed to play down the indication which sleep disturbances may provide of environmental influences The established co-variation with prolonged speech impediments should presumably be interpreted as indicating a stress factor in the background as should the fact that children who have had to be separated from their parents and put in a strange environment (another private home a children s home or a hospital) are represented to a large and statistically significant extent among those suffering from sleep disturbances

A small child who wakes up during the night generally wants something from those around it This is still more true during infancy and the following year when children attract attention by crying A child of 4 or 5 on the other hand, is less disposed to cry in order to obtain the security it seeks after waking up during the night As a result its parents suffer less inconvenience even if the child seeks its security in their beds Many mothers in this sample have testified to the furtive and almost inconspicuous way in which their children climb into bed with them. Sometimes the mother does not wake up when the child comes but discovers him in bed with her later in the morning Sleep disturbances in the sense of inconvenience to the family are far less frequent around 4 - 5 years than earlier at the same time as the frequency of night wa-

king is still remarkably high and differs little from previous years. This observation is corroborated by experience of work at child welfare centres A 4 or 5-year-old child is less likely to be accompanied by the exhausted haggard mother so frequently associated with the lively night-waker of twelve months

Parental response to night waking

The most effective means of getting wakeful three-year-olds back to sleep for the rest of the night was found to be to let them sleep with their parents This is still the main resort at 4 and 5 years The next most frequent resort is to attempt to settle the child by talking to it giving it something to drink tucking it in and making a fuss of it A few mothers report that they have punished their children or scolded them but nobody finds this an effective remedy Irritation and anger are less common in the account of remedies tested Waking has been ignored in 3 % of the methods considered effective at 4 years Sedatives seem by all accounts to have been used very seldom. Of the 6 cases reporting their use half considered them to be ineffective Even for those who tested a variety of methods the parental bed was generally the ultimate resort How common this is can be seen from Table 5 on page 166.

SOMNAMBULISM

INTRODUCTION

Any direct link between dreams and sleepwalking has been considered disproved ever since EEG and EMG investigations were used during the mid-1960s to prove that somnambulism never begins during REM sleep (1 3 4) The old idea of sleepwalking as action due to the influence of dreams is also hard to reconcile with the inability of the sleepwalker to recall any dreams in connection with the event Neuro-physiological discoveries have prompted the question whether sleepwalkers are not more awake than asleep (4 5) It has not been possible to ascertain any reason for the sleepwalker acting as he does. Even if neuro-physiological discoveries have ruled out dreams as the precipitator of this species of coordinated muscular activity the question still remains why somnambulism is commoner in certain mental states than in others (9) The comparatively higher incidence in children as compared to adults is thought to be connected with an organic immaturity factor The statistically significant rise in frequency of sleepwalkers to be found in their parents as children has been presumed to indicate a genetic predisposition for the condition.

The information given by the mothers in this study during regular structured interviews concerning their children s sleep deviations make it possible to test certain statistical relations between variations and deviations in sleep behaviour The material can be suitably applied to the question whether somnambulism co-varies directly with other notable forms of behaviour exhibited by the child in connection with sleep Attention here will above all be devoted to the statistical relations between somnambulism and bad dreams.

Method

Data concerning somnambulism were first collected at 6 years (V: item 23) The answers are graded according to frequency on a five-point scale: never seldom, sometimes often always

Frequencies in the "bad dreams variable at 6 - 8 years of age have been noted on the same five-point scale as somnambulism (no seldom, sometimes often and always) The last of these categories was not used in any of the answers. Mothers were also asked to give examples of dreams

RESULTS

Somnambulism, Frequency, Persistence

Since there is no difference between the sexes girls and boys have been counted together The percentage incidence in cross-sectional investigations at 6 - 8 years is shown by the following table

Table 12. Incidence of sleep-walking at 6 - 8 years of age
Percentage distribution. Cross-sectional

Age in years	Seldom	Sometimes	Total
6 (n=200)	5 5	3 5	9
7 (n=192)	4 6	5 2	10
8 (n=194)	6 6	5 6	12

Approximately half the children noted for somnambulism during the three-year observation period 6 - 8 years had been reported as only seldom" suffering from this condition and at no more than one annual investigation. This group numbers 19 children. The remainder (=18) have been noted for the symptom at two or more of the three annual investigations The maximum incidence within this group is represented by 5 children classified sometimes" at all three annual investigations Thus no children walked in their sleep often or always" It is hard to convert these designation into a fixed number of nights per month: the scale reflects the mothers own interpretation of the expressions Fig 5 shows the prospects of a child who walks in its sleep at 6 years continuing to do so during the years immediately following.

All the children (seldom + sometimes) awarded a plus rating are included here Only children investigated every year are represented (pure sample)

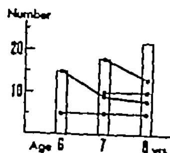


Fig 5. Persistent sleepwalkers (curve) in relation to cross-sectional number(bars).Pure sample

——— = seldom + sometimes

- - - - = sometimes

As can be seen from fig 5 somnambulism also occurs as a sporadic phenomenon for a year or so and then disappears. Persistence during the observation period is more conspicuous when the symptom has appeared more frequently (the broken line in fig 5)

Bad dreaming, Frequency, Persistence

The distribution between different frequencies is shown in the table In the absence of any statistically significant difference between the sexes boys and girls have been counted together

Table 13. Incidence of "bad dreams at 6 - 8 years of age Percentage distribution. Cross-sectional

Age in years	Seldom	Sometimes	Often
6 (n=200)	32 5	18	1
7 (n=192)	37	17	1
8 (n=194)	41	15	0 5

The development and persistence of the symptom in the same individuals during the period 6 - 8 years is illustrated against the background of the cross-sectional figures in fig 6



Fig 6 Persistent bad dreaming" (curves) in relation to cross-sectional number (bars) Percentage distributions Pure sample

Thus according to the mothers reports it is not particularly common for the symptom to remain a prominent feature of the child s dream life for a matter of years It is more temporary than persistent Six-year-olds having nightmares are only troubled by them to a slight observable extent at 8 years

COVARIATION OF SOMNAMBULISM AND BAD DREAMS

The simultaneous occurrence of somnambulism and unpleasant frightening dreams is shown by the following table

Thus somnambulism occurs in the same children together with frightening dreams to a greater extent than can be attributed to chance

Table 14. Simultaneous occurrence of somnambulism and bad dreams at 6 7 and 8 years. X^2 calculated with Yate s coefficient

Somnambulism (seldom" or sometimes")		Bad dreams sometimes or often Yes	No	X^2-test	Significance
6	yes	4	14	negligible	-
	no	34	148		
7	yes	8	11	= 6 688	01
	no	26	147		
8	yes	10	14	= 16 320	001
	no	16	154		
Somnambulism sometimes between					
6-8	yes	9	5	= 5 647	02
	no	53	127		

DISCUSSION

The habit of sleepwalking and trouble with unpleasant dreams are often a temporary and episodic phenomenon among the children in this sample If they occur simultaneously to such an extent as to suggest more than coincidence one is moved to seek some kind of connection between them. It is unlikely that mothers interpreted sleepwalking as a nightmare activity because when they quoted examples they did not relate the dreams they described to somnambulism. Probably the same background factor that initiates sleepwalking has on other occasions brought about the frightening contents of the children s dreams This observation agrees well with that reported in our introduction, namely that somnambulism appears to be more common in certain mental states than in others (9) At the same time however it should be remembered that temporary somnambulism, which cannot be regarded as a habit occurs more frequently in "normal than has hitherto been realised.

SUMMARY

An account is given of a follow-up of sleep behaviour between the ages of 4 - 8 years in c 200 randomly selected children in the longitudinal Stockholm study Average sleep durations and their standard deviations are calculated for different ages against the background of sleeping and waking times The correlation between the duration of sleep in the same children at different ages is far better than that between the ages below 3 years but the correlation coefficient does not exceed 50 for any of the ages compared.

Between 10 - 15 % of the children have bedrooms of their own. In c 25 % of the families one or both parents are still sharing a bedroom with the child when the child is 8 years old while below that age the proportion is far higher All the children have a sleeping place of their own but a strikingly large number still spend a certain proportion of the night in their parents beds At 8 years the percentage has fallen to 18 % It is statistically probable that this occurs more frequently in social group 3 The mother s employment status would appear to be immaterial

Reluctance to go to bed is often a characteristic reported in the same children year after year The same applies to night waking. The frequency of troublesome night waking diminishes from year to year A distinction should be made between night waking and sleep disturbances Most children waking in the night (at 4 and 5 years) show no sign of fright but rather a need of playful attention. The majority of cases of night waking are thought to be related to physiological variations in the depth of sleep rather than to mental imbalance The placing of children in strange surroundings covaries with subsequent night waking Persistent night waking and prolonged speech impediments occur simultaneously too often to be attributed to chance A study has been made of the occurrence of somnambulism and unpleasant dreams between the ages of 6 - 8 years. Approximately every tenth child is reported to walk in its sleep occasionally at the age of 7 In cases where the symptom has manifested itself more frequently it has shown a marked tendency to

persist Unpleasant frightening dreams do not seem to recur regularly in the same child to any considerable extent but as a symptom they are more frequent than somnambulism. Both symptoms occur simultaneously in one and the same child at the ages of 7 and 8 considerably more often than can be attributed to chance ($p = < .01$ and $< .001$ respectively)

REFERENCES

1 Broughton, R.: Sleep disorders: disorders of arousal? Science vol 159 1070 1968

2. Dement V C and Kleitman N : Cyclic variations in EEG during sleep and their relation to eye movements bodily motility and dreaming. Electroenceph. Clin. Neurophysiol 9: 673 1957

3 Fisher C and Dement W : Studies on the psychopathology of sleep and dreams Amer J Psych. 119: 1160 1963

4. Jacobson, A. and Kales A.: Somnambulism: All night EEG and related studies In sleep and altered states of consciousness. Res. Publ Ass. nerv ment Dis vol XLV Baltimore 1965

5 Kales A. et al: Somnambulism: Psychophysiological correlates Arch. Gen. Psychiat 14: 586 1966

6 Klackenberg G : The sleep behaviour of children up to three years of age Acta paed. scand. suppl 187 105 1968

7 Klackenberg G et al: The social background and its changes during the children s first three years of life Acta paed. scand. suppl 187: 28 1968

8. Nagera H.: Sleep and its disturbances Psychoanalytic study of the child, vol XXI 1966

9 Orme, J M.: The incidence of sleep-walking in various groups. Acta psych. scand. 43: 279 1967

CHAPTER XV

TEMPER TANTRUMS AND DESTRUCTIVENESS

T E M P E R T A N T R U M S A N D D E S T R U C T I V E N E S S

INTRODUCTION

The following essay is concerned with the frequency and changeability of these symptoms up to the age of 8 years in a randomly recruited group of children. Since both variables have been used in different contexts in the present study of the symptomatology of children, a simple account of their incidence is called for together with an illustration of their co-variation.

Children often display their despair anger or disappointment expressively and immediately by means of physical action. Outbursts of this kind can take various forms but they are all vehement immediate and patent expressions of frustration due generally to a sudden obstacle a restriction of the child s possibilities of fulfilling its wishes The action is more often than not provoked by the prohibitions or other actions of the person or persons in the child s immediate surroundings but outbursts may also be due to physical impediments or failures in play

What is interpreted as destructiveness during childhood is often a mixture of lack of wisdom, incapacity inquisitiveness and vandalism. It may be difficult to identify the underlying factor among those however we can probably assume that a conscious desire to destroy becomes relatively more predominant with age In view of the difficulty of demarcating the character of this symptom, the frequency study described below has been confined to data from between 4 and 8 years

Method

The children s propensity for temper tantrums has been described every year (interview form VII item 54 - 57 at 4 - 5 years and questionnaire V item 62 at 6 - 8 years) The multigrade scale of the *average frequency* of serious outbursts per day or other unit of time makes it possible to differentiate Instances of the character and content of the outbursts are entered on the basis of a standardised interview As can be seen from the following there were many alternatives to choose from: lies on floor, stamps slams *doors* hits *inanimate objects* hits peopl about throws things screams bites rigid, thrashing limbs hits hurts self blue in face This exemplification of outbursts of temper given

by the mother made for greater certainty in the evaluation of the symptom.

The graduation used at 1 2 and 3 years (usually sometimes, rarely or no) cannot however be transposed directly into the more differentiated specification of frequency used in subsequent years This is marked in the frequency curve by a break.

Symptom persistence has been calculated for a "pure sample i e excluding children who were absent from any of the investigations Since frequency data at 4 years and subsequently are described in the same terms, the longitudinal account has been confined to the ages of 4, 5 6 7 and 8 years

The mother s opinion of her child s destructive tendencies is given in interview form VII: 58 - 59 at 4 - 5 years and V: 57 at 6 - 8 years A trivial difference in the phrasing of the question reflects something of the initial uncertainty surrounding the content of the symptom. At 4 - 5 years the mother is asked: Is he a destructive child? and at 6 - 8 years: Does he break things on purpose? The more deliberate form of destructiveness which is of greater interest in the assessment of personality should be more accurately reflected by the mothers answers at the later ages Alternatives given at the 4 and 5-year-old interviews include: tears paper tears books defaces walls/books takes things to pieces pulls stuffing out of dolls/furniture throws toys in temper breaks things for pleasure clumsiness

At 4 and 5 years the incidence of the symptom is graded as follows: definite habit moderate habit occasionally never At 6 - 8 years: always often sometimes seldom, never A child coming in the definite habit class at 4 - 5 years is equated with children in the always" or often classes at 6 - 8 years for estimates of symptom persistence Similarly "moderate habit and sometimes have been taken as representing the same frequency

RESULTS

The frequency of temper tantrums

Fig 1 shows the percentage cross-sectional incidences of the symptom between the ages of 1 and 8 years. The percentages in the right part of the curve denote the occurrence of daily outbursts of temper tantrum, while the left part represents all denoted "usually

There is no demonstrable sex difference in the number of children noted for outbursts at least once every week at any of the ages tested (2 - 8 years) The curve have therefore been made to include both sexes together

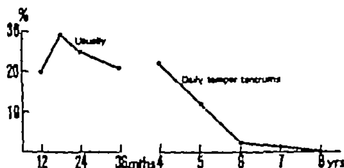


Fig 1 Frequency of children with temper tantrums at various age
Cross-sectional percentage distribution

Frequency of destructiveness

Fig 2 shows the cross-sectional frequencies for different ages (4 - 8 years) Separate curves are drawn as the sex differences proved significant (see below)

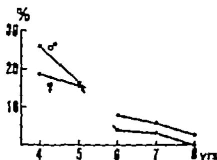


Fig 2 Frequency of children with destructiveness at various ages
At 4 - 5 years: d finite habit
6 - 8 years: often alway
Cross-sectional percentage distribution

As can be seen from the curves boys are considered more active at all ages in pulling things to pieces The frequency differences are statistically significant both at 4 years and at 6 – 8 years (p = 02) For this comparison the destructiveness variable was widened to include children with a moderate habit as well as those with a definite habit

The persistence of temper tantrums

Fig 3 shows how the intensity of daily unrestrained temper tantrums expressed in frequency declines and disappears relatively quickly after the age of 4 years The curve in the lower picture denotes the persistence of the symptom the bar its cross-sectional frequency The upper picture illustrates changes in the degrees of frequency between 4 and 8 years By 8 years the outbursts have either disappeared or become less frequent

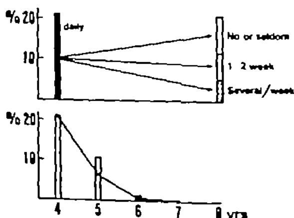


Fig 3 Frequency of daily temper tantrum at various ages
Below: Persistence curve in relation to cross-sectional bars.
Above: Changes in intensity of the habit in children with daily outbursts at 4 years
Percentage distribution in pure sample

The persistence of destructiveness

Corresponding data concerning the persistence of destructiveness are given in fig 4.

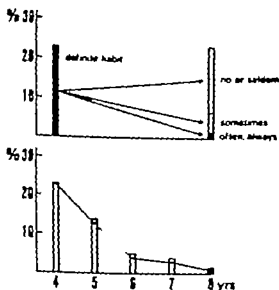


Fig 4. Frequency of destructiveness at 4 - 5 years = definite habit at 6 - 8 years = often always"

Below: Persistence curve in relation to cross-sectional bars.

Above: Changes in intensity of the habit in children with definite habit of destructiveness at 4 years

Percentage distribution in "pure sample

Covariation temper tantrums - destructiveness

The X^2 value for the covariation of daily temper tantrums and definite habit of destructiveness at 4 years is 4.615 ($p = .05$)

No similar covariation has been established between the less frequent forms of temper tantrums and destructiveness occurring at 8 years.

DISCUSSION

It is obviously very common during early childhood for children to express their feelings by physical activity of the kind termed temper tantrums The tempestuous movements thus generated during the first years of life are not really directed at any particular target The child strikes out, thrashes stamps screams or throws itself into the floor using its entire body to vent its feelings Sometimes adults can establish contact to pacify and comfort the child sometimes they cannot Gradually the outbursts assume a more deliberate and specific character with sudden anger being directed at a particular person or object The boundary between aim-directed destructiveness and uncontrolled bodily activity may disappear By 4 years there exists among the children in the sample a covariation of daily temper tantrums and notation for habitual destructiveness which is probably not just coincidental Although some children are noted for daily temper tantrums unaccompanied by destructiveness it can be difficult for the mother/observer to distinguish between unintentional and deliberate destructiveness

Temper tantrums are a predominantly age-conditioned symptom. Their frequency steadily declines once the 4-year mark has been passed. Children with daily outbursts become increasingly rare None of the children in the "pure 4 - 8 years sample retain the same intense frequency at 8 years In the case of a minority of the children with daily temper tantrums at 4 years the symptom has disappeared entirely by 8 years while 59 % are still liable to react in this way though they do so less often This may be because most children have learned that parents or siblings do not appreciate outbursts and destruction of this sort It may also be connected with an increased tolerance towards the factors provoking the outbursts a tolerance which has developed not only in the child but also in its surroundings It may also be due to a reduction in the number of occasions calculated to produce friction, owing to the considerable periods of time which the 8-year-old spends outside the home However this may be temper tantrums in children of 7 - 8 years would appear to have an altogether more distinctive significance than their counterparts at the ages of 3 - 4 years

SUMMARY

The temper tantrum and destructiveness symptoms are described with regard to frequency sex difference persistence from 4 to 8 years and co-variation. Both symptoms show a steep decline in frequency after the age of 4 years The boys are reported as being more destructive than the girls ($p =< 02$) There is no sex difference as regards temper tantrums There is a certain co-variation between the symptoms at 4 years ($p =< 05$) but no such co-variation can be established at 8 years

CHAPTER XVI

T I C S   I N   S T A T U   N A S C E N D I

T I C S I N S T A T U N A S C E N D I

INTRODUCTION

The tics symptom is generally defined as consisting of rapid involuntary apparently purposeless and frequently repeated jerks in certain functionally co-ordinated muscles or groups of muscles The forms of expression are versatile and varied The most noticeable and perhaps the commonest form of tics involves certain groups of muscles in the face and neck. Blinks with the facial muscles round the eyes nasal and labial movements and grimaces of various kinds turns of the head and shoulder shrugging are thought to be more common than sound tics produced by functional deviations in the passage of air through the larynx palate and nose The commonest pattern of tics over the different parts of the body seems to be such that children with tics symptoms which occur at the greatest relative distance from the face tend to have more tics in nearby groups of muscles too so that in this sense they are more severe

The general fidgeting and exaggerated muscular activity occurring in certain children during childhood (in some cases with definite atato-tic-atactic element due to brain damage) is distinguished by definition from tics by the speed with which a limited group of muscles (as with tics) is stimulated to action. Misinterpretation together with ignorance of the manifestations of the hyperkinetic syndrome during infancy can sometimes lead to a confusion of the two

A prospective longitudinal study is especially calculated to draw attention even to minor forms of deviation Often a phenomenon will start with slight symptoms which are practically indistinguishable from normal behaviour later appearing and perhaps becoming set in a manifestly more substantial symptom of deviation Consequently if certain observations are continually registered and ventually assume the form of a well-defined symptom, it should be possibl to evaluate early symptoms according to subsequent discoveries

The present say i concerned with the occurrence of tic-like symptoms up to the age of ight years and with the persi tence and deve-

//

lopment of the symptom Finally we shall consider whether there are any clear links between tics and other symptoms of emotional tension.

RETROSPECT OF EARLIER INVESTIGATIONS RELEVANT TO THIS STUDY

Doubts have been expressed as to whether tics can be diagnosed as early as the pre-school stage Seven years has been specified as the minimum age limit Tic-like muscular movements at earlier ages are regarded as an undifferentiated nervous habit in a child with considerable motor unrest In his textbook of child psychiatry Kanner (10) states that the youngest child with tics observed by him was six years old. A rise in frequency during school age up to 11 - 12 years is regarded as typical of the symptom being succeeded by an appreciable decline in frequency Other writers have described typical tic symptoms in pre-school children (5 6 11) Another view is that tics attain their maximum frequency at the ages of 6 - 8 years (2 14) Between 70 - 90 % of clinical cases can be traced back beyond 10 years (14 11) Prevalence is indicated with a considerable variation ranging from 4 5 % in 10 to 11-year-old boys and 2 6 % in girls of the same age (8) to 23 % of schoolchildren without any further specification of age (1)

According to Kanner tics are a symptom of emotional tension which always occurs in combination with other behavioural deviations a rule to which no exceptions are known A happy secure child never develops tics Mahler (11) interprets tics as an incipient neurosis or as part of the symptoms and the visible expression of an established psychoneurosis She also advocates a distinction between these forms and the state of severe tics in which the symptom it self represents the central and essential disturbance a psychosomatic disease of the motoric system (maladie des tics) Other psychoanalysts have put forward the opinion that the symptom constitutes a masturbation equivalent (4 12) In other quarters the cause has been defined as organic in the form of damage to the striopallidal system resulting from encephalitis or some other form of brain damage (7 13) Some psychologists have espoused the theory that tics are an established conditioned reaction that can be eliminated by negative reinforcement

Clearly the tics symptom has given rise to a wide variety of interpretations Authors writing from the point of view of depth psychology and describing the treatment of individual adult patients find the symptom deeply rooted and difficult to treat (4) A similar attitude can to a greater or lesser degree be discerned among those who have worked with children (11) Although the symptom can disappear quite independently of treatment (16) it can also return to a certain extent after some months or years as a characteristic selected symptom of emotional release in the individual concerned In a follow-up investigation of 220 Danish children on average 9 years afterwards 50 % of the cases were found to be cured i e without symptoms for at least a year (14) The prognosis was worst in cases where a close relative exhibited the symptom simultaneously In a Swedish clinical follow-up investigation of 29 tiqueur children in 1963 two-thirds were found to be free from symptoms (9) The same results were reported from a German investigation as early as 1930 (2) The latest contribution (3) (1969) a follow-up investigation of 89 tiqueurs emphasizes that a long period of observation should be allowed to elapse before giving the proportion of recoveries In this investigation too two-thirds of the cases had completely recovered from the symptom The observation period amounted to 8 years or more

THE FREQUENCY PERSISTENCE AND NATURE OF TICS

Method

Assessment of the occurrence of the tics symptom in the children in this study is primarily based on interview statements (form VI item 20: 0 - 9 at the ages of 2 - 5 years and questionnaire V: item 57: 0 - 4 at the ages of 6 - 8 years) The question put to the mother when the child was investigated between the ages of 2 - 5 years was worded as follows: Have you seen any blinkings jerks or grimaces? This was rephrased slightly for the interviews made between the ages of 6 8 years: Have you seen any jerks blinkings ti or other nervous" movements? Apart from typical tics as defined before only such habitual and sudden muscular activity as has been considered involuntary has been included. This limitation in evaluating the answers applies first and foremost to the conditions referred to as grimaces Whether grimaces are apparently spontaneous or constitute an involuntary individually developed response reaction to definite emotional experience the boundary between them and the classical forms of tics is unstable The check has in most cases been supplemented by a description of the itutions in which the reaction mostly occurred during the ages of 2 - 5 years This has made it possible to assess the child s emotional i[illegible]

It should however be noted when evaluating the results that the distinction posed by given definitions of tics between definite cases and nervous jerks of a more undifferentiated variety is uncertain with regard to children aged 6 - 8 years owing to the scantier descriptions of symptoms noted for these ages

Other variables included in the interview with the mother and used to shed light on the tics symptom are motor unrest temper tantrums speech impediments somnambulism and masturbation. The content of these variables will be described as they are utilized

Results

None of the children mentioned below as tics cases has exhibited neurological brain damage in the simultaneous pediatric investigation

The youngest child in whom unmistakable eye tics were recorded was 1½ years old It had been troubled with blinking for several months The symptom disappeared for several years but returned with renewed strength several times daily at the age of six to a somewhat lesser extent at 7 years and sporadically at 8 Another child investigated at the age of 2 had been troubled by involuntary nasal spasms and blinking for the preceding 3 months



Fig 1 The frequency of tic-like symptoms at different ages
Percentage distribution

Fig 1 shows the percentage frequency at different ages from 3 to 8 years It should be noted that to begin with the symptom appeared

only temporarily i e for short periods sometimes never recurring during the observation period up to eight years It should also be emphasized that the tic-like symptom is generally mild thus differing from clinical cases In the great majority of cases it consists of symptoms from the region of the eye

Table 1 shows how intermittently the "nervous jerks occurred.

Table 1 The intermittent occurrence of the symptom.

Reported at one annual investigation	35 cases
Reported at two annual investigations	16
three	8
four	4
" five	2
six "	1

The symptom occurred between the ages of 7 - 8 years in rather less than half the children who exhibited it for only part of a single year To obtain a better picture and perspective of the figures in the above table which exaggerate the intermittent nature of the tics symptom, one must venture outside the period covered by this essay to trace the occurrence of the symptom at later ages in people whose first period occurred between 7 - 8 years. School age is generally regarded (see Kanner) as the period during which the symptom most frequently appears A comprehensive account of this period will not be possible until all the children have passed the appropriate age A preliminary follow-up of the children whose nervous tics began at 7 and 8 years shows that most of them also exhibited the symptom later on during their school years.

The difference between the sexes is significant at the 5 % level if all the children exhibiting symptoms at one time or another during the observation period up to 8 years are included. The boys predominate This agrees with results obtained in a number of other reports (5 11 14)

The tic-like movements exhibited by the children in the sample up to the age of 8 years have mainly consisted of blinkings of the eyelids alone or in combination with contractions of the outer muscles of the eyes Nose twitchings persistent and unnecessary clearing of the throat and shoulder shrugging are also represented in the group If the tic symptom returns after having disappeared for a time it tends to assume the same form as on the previous occasion. When the symptom persists year after year as happened in some cases its basis is extended to include additional groups of muscles An example of this is provided by a girl who had eye tics at 3 years 4 years and 5 years At 6 years she was reported as having shoulder shruggings, head turnings and throat clearing as well as blinking A boy with blinikngs continued later on with nose twitchings and lip-licking

DISCUSSION

The main impression on examining the longitudinal symptom chart of the different tiqueur children is that in the majority of cases the symptom occurs during limited periods which are sometimes separated by one or more years without symptoms What ultimately sets in the form of an occasionally mystifying habit has been demonstrated less prominently and expressively during the child s pre-school years as a reaction tendency of the same kind. It is also typical of the pattern that of the relatively large group of children with sporadic symptoms only a minority ultimately develop a condition that could be termed neurotic As long as the symptom is mild and reversible - as it is in the majority of pre-school cases - it should be regarded as a reactive stress symptom. Prognosis and symptom development are dependent on the intensity of the environmental factor to which the symptom constitutes a reaction. Only a very few children in this sample have retained the symptom uninterruptedly during the observation period from the appearance of the very first signs up to the age of eight years Even in these children the frequency-intensity is reported as varying during the period between the annual investigations

The symptom is sometimes stated to have begun in connection with a specified emotional reaction later recurring habitually and without any clear relation to any particular known experience The context

leads one to suspect that what began as a shielding or evasive movement has since become automatic Thus according to the psycho-dynamic view the muscular emotional reaction serves a definite initial purpose If the motivation is removed, the symptom will disappear more easily when it occurs during the period of development preceding the creation of a super-ego This might explain the episodic and sporadic nature of the symptom during early childhood The phenomenon disappears relatively easily at these ages and is incorporated in the pattern of reactions and fixed in automatism if the environmental pressure continues up to an age when the super-ego takes over and consolidates the reaction

Since data on which an interpretation of the origin of the symptom can be based have not been systematically sought in this statistically oriented study the above reflections are based on individual cases. The case histories of psychoanalytical literature describe several children of school age who have exhibited fairly acute tics of various kinds in connection with severe emotional stress (6 12) In these cases the experiences chronologically related to the appearance of the symptom imply that the remaining tic symptom originally has an expressive content

THE RELEVANCE OF EMOTIONAL FACTORS

INTRODUCTION

Most of the cases of tics occurring in adult life originated during childhood A child employs muscular movements to express its feelings and impulses in a far more immediate and obvious way than adults Affect motility or general motor unrest is often a direct reflection of a feeling of pleasure or displeasure excitement anxiety or aggression. The relative sub-cortical domination of motility during infancy is gradually superseded by the deliberately controlled cortico-pyramidal part of the central nervous system. The pressure put on the child by its environment to curb its muscular unrest leads the child to try to suppress it The conflict resulting from the discrepancy between the need for affect motility and the sanctioned means of expressing emotion paves the way for the development of tics

Deliberate control is connected with the development of the ego and its functions of bodily control When eventually the super-ego assumes most of the role of the environment (for which read the parents) the symbolic movement will unless equilibrium has been achieved in the meantime deepen into a neurotic symptom instead of the less persistent reactive symptom it originally was

Mahler (12) has particularly stressed the connection between the child s unrest and other motor expressions of affect on the one hand and tics on the other According to her in the behaviour of children with tics it should therefore be possible prior to the appearance of the symptom to trace definite symptoms of the inability of the ego to control the emotions It is not unusual for the case history of a schoolchild irrespective of the psychic difficulties concerned to include records of earlier outbursts of rage Temper tantrums are far too frequent at 2 - 3 years to be particularly distinctive The symptom must therefore be graded and this is not easily done post facto

The present longitudinal sample affords a certain opportunity of testing the main lines of Mahler s hypothesis (by statistical compa-

rison) concerning the relation between the early incidence of motor unrest exceptional liveliness and poor control of the emotions on the one hand and the subsequent appearance of tic-like symptoms on the other

Method and material

The evaluations and observations compared in the tests of statistical significance concern the extent to which the extreme cases of muscular unrest between 3 - 5 years are relatively more represented in children with muscular twitches and grimaces at 6 - 8 years than among the other children in the sample of the same age Each annual interview includes data concerning whether mothers found their children calm or lively (form VII item 75) At 3 years the graduation is as follows: restless lively medium calm while at 4 and 5 years it is: restless lively quite lively medium, fairly calm and calm. There is no uniform objective scale for symptom evaluation of this kind but the data ought nonetheless to reflect genuine differences in the behaviour of the children in the extreme groups. It is unlikely that the majority of children at one end of the distribution curve would have been placed at the other extreme by another judge Thus the data were collected on average three years before observations of nervous jerks were reported The jerks occurring at the latter juncture and confined to certain groups of muscles are markedly different from general muscular unrest

Children described as restless at some stage during the observation period 3 - 5 years have been placed in one comparative group A tentative examination was first made of the result of a comparison with the other extreme group referred to as calm. The other variable consisted of children who had had tic symptoms at some point between the ages of 6 - 8 years Frequency was not considered in the tics variable the comparison being concerned with the presence or absence of symptoms

Results

9 girls and 15 boys were lassed as restles in one of the three annual investigations at 3 4 or 5 years The corresponding numbers of calm children were 18 and 27 respectively Between these extremes came the other children with various degrees of slight restlessness and qualified calm. On an average of three years later tics symptoms occurred more frequently in the restless children than in the calm ones In a X^2 estimate the difference for both sexes taken together was ignificant at the 5 % level

After this tentative preliminary comparison an stimate was made using the entire sample The restless children were related to the rest with regard to the occurrence of tics Here too it was found

that the group of children noted at an early age as being particularly restless were more prone to develop tic symptoms subsequently than the other children ($X^2 = 6\ 923$)

If the group of 4 and 5-year-olds with a propensity for outbursts of temper is compared with the other children of the same ages regarding the subsequent occurrence of tics between 6 - 8 years no probable significance is obtained for the existence of any difference The X^2 values are negligible for both boys and girls The same negative result is obtained when children with exceptional outbursts of anger between 6 - 8 years are taken as a comparison group instead of the 4 - 5-year-old temper tantrum children. Not even these children have tics any more frequently than other 6 - 8-year-old who are able to control their tempers

15 girls and 16 boys have exhibited a persistent tendency to temper tantrums between the ages of 4 - 7 years i e they have been noted for recurrent outbursts of exceptional vehemence during these years There is no demonstrable relation in these groups to the occurrence of tics at 4 - 8 years

DISCUSSION

* As we have seen the somatic investigation revealed nothing to suggest cerebral neurological damage in children exhibiting tics symptoms between 6 8 years of age The general restlessness exhibited by a large number of them between the ages of 3 and 5 years is therefore assumed to express an emotionally initiated stress factor This is interpreted as a disturbance in the child s equilibrium regardless of whether it is a constitutional weakness individual predilection or unusually strenuous experiences of environment that produce the increase in motility Episodes of manifest tension limited to certain groups of muscles are more likely to follow a year or more later in this group than in the group of more calmly behaved children. This is the relation whose probability it has been possible to establish There are also six to eight-year old children with tic symptoms whose parents have always found them motorically calm and whose tic symptoms have developed so discreetly that they have not been preceded by any visible outward motility disturbances One

might perhaps venture to simplify the equation by surmising that the general "muscular language of the younger child provides an indication of greater risks of changing into an involuntary attitude language in the older child when movement is restricted and inhibitions develop

At the same time one finds no demonstrable frequency correlation between outbursts of the temper tantrum type and contemporary or subsequent tic symptoms The theory which might be based upon this observation is that both temper tantrums and tics provide substitute outlets for increased emotional tension.

CO-VARIATION WITH OTHER VARIABLES

INTRODUCTION

If the tics symptom is regarded as a symptom of emotional tension there may exist co-variation with other expressions of manifest reactive psychic or neurotic symptoms which include motoric elements Somnambulism stammering and nail biting have been chosen as examples of such behaviour This does not imply the precipitate assumption on the author s part that the individual s choice of reaction to stress should primarily be based on such simple rules that reactions with motoric elements accompany one another The choice of these symptoms for purposes of comparison has among other things been due to the fact that psychic conditions such as somnambulism speech impediments and nail biting need not raise questions of interpretation as to whether these phenomena exist or not The habit of playing with the genitals has also been related to the tic symptom.

Method

Observations concerning somnambulism its occurrence and frequency have been described in the essay on sleep and sleeping habits in children aged between 4 - 8 years Systematic collection of data on children suffering from nocturnal restlessness with elements of somnambulism were first collected at the age of 6 years All the children exhibiting this symptom between 6 - 8 years regardl of its frequency (which was generally low) have been included in one comparative group the other group comprising children who have never suffered from this kind of nocturnal restlessness The occurrence of tics in both groups at corresponding ages has been tested for significance (the item numbers for variables of somnambulism are V:23: 0-4 at 6 - 8 years)

as regards the nail biting variable all the children exhibiting the symptom between 6-8 years as well as the children belonging to the group of habitual and persistent nailbiting have been compared in two separate tests with the symptom-free children for the occurrence of tics (item numbers V:33: 0-4 at 6-8 years) The composition of the group of habitual nail-biters is described in the report on nail biting

The stammering variable has been studied and described in the essay on speech impediments The impediments involved are generally slight ones such as stammering (items V:46: 0-4 at 6-8 years)

Playing with the genitals is a common phenomenon particularly among boys The children who have indulged most conspicuously and frequently in this activity have been selected for study as a comparative group Since for natural reasons this habit is more common among boys than among girls the division has been made on a different basis The degrees of frequency given in form V: 36 ranged from 0-4 (= never 1 = seldom, 2 = sometimes 3 = once or twice daily and 4 = several times daily) The boys marked 2 3 or 4 in at least two of the annual investigations between 6-8 years formed one group while the remaining children formed the other In order to obtain a sufficiently large girls group all those who at some time during these 3 years (6-8 years) have been marked 2 have been separated from the others At this age none of the girls exhibited any noticeable daily interest in her genitals

Results

The significance tests of co-variation have been collated for the sake of simplicity in Table 2

DISCUSSION

The results are very much as expected. The non-fluency in speech appears primarily in conditions of emotional stress The manifestations of tics are also aggravated in nervous and tense situations It is to be assumed that the same ingredient of emotional tension is present in both symptoms During the observation period 6-8 years the symptoms appear in one and the same individual sufficiently often not to be dismissed as mere coincidence But the question remains why the choice of symptoms sometimes affects the speech and sometimes the contact furnished by the body language

Little is known concerning the deepest causes of somnambulism. This co-variation may indicate that it is a reaction to the same emotional disturbances as give rise to tics

Table 2 The co-variation of the tic symptom with other variables

Variable		χ^2		p
Tics/stammering at 6–8 years	♀	6 163		02
	♂	7 504		005
	♀ + ♂	14 450		001
Tics/somnambulism at 6–8 years	♀	0 417	(yates corr)	-
	♂	4 647		05
	♀ + ♂	5 157		025
Tics/nail biting at 6–8 years	♀	negligible		-
	♂			-
	♀ + ♂	1 616		-
Tics/"masturbation at 6–8 years	♀	12.427		001
	♂	negligible		-
	♀ + ♂	4 948		05

It is not surprising that no demonstrable relation is revealed to the nail biting symptom which is probably of a different etiological nature Nail biting is probably more closely related to defence reactions than tics which contain a larger element of anxiety and fear

It is difficult to explain why there is a definitely significant co-variation with genital play among girls but not among boys Possibly boys with habitual or compulsive behaviour were not sifted out closely enough to distinguish them from the rest The borderline between habits of a greater or lesser degree of compulsiveness is vague in both sexes but it may be that attitudes to this behaviour vary according to whether the child concerned is a girl or a boy If girls frequently play with and probe the vulva tract their behaviour attract more attention and perhaps greater disapproval Those who nonetheless persist at the age in question may be assumed to demonstrate a greater element of compulsion than the others

SUMMARY

Tics or tic-like symptoms in children in a longitudinal growth study have been described with regard to frequency and persistence up to the age of 8 years The tic symptom is more common in boys than in girls In the ages studied it mostly occurs episodically but there are cases where it can be demonstrated to be permanent from the age of 2 years Tics occur most frequently in the region of the eye to begin with When the symptom has persisted for some time it can extend to other functionally co-ordinated groups of muscles

The relation of the tic symptom to motor unrest due to emotional causes and to temper tantrums has been studied A significance test has been carried out to ascertain whether children exhibiting these symptoms between 3-5 years tend more than others to develop tic symptoms between 6-8 years It appears probably ($p = 05$) that younger children with motor unrest are more liable to develop tic symptoms a few years later than children reported as being of a calm disposition On the other hand it cannot be established that children with temper tantrums are more prone than others to react with a tic symptom.

The co-variation of the tic symptom with stammering and somnambulism in the ages of 6-8 years is significant at least at the 2 % level There is also a strong co-variation in girls who at this age indulge i play with their genitals more conspicuously than other children The same cannot be established for the boys Nail biting does not display any relation to tics

REFERENCES

1 Albrecht H.: Über die Ticerscheinungen im Kindesalter Nervenarzt 20:314 1949

2. Bonhein C: Über den Tic im Kindesalter Klin Wochenschr 9:2005 1930

3. Corbett J Mathews A.H. Conell P H. and Shapiro D A.: Tics and Gilles de la Tourettes syndrome: A follow-up study and critical review Brit J Psychiat 115:1229 1969

4 Ferenzci S: Psychoanalytic Observations on Tics in Further Contributions to the Theory and Technique of Psychoanalysis Hogarth 1921 cit after Gerard

5 Freud A. and Burlingham D T: War and Children International Univ Press 1943

6 Gerard Marg.: Psychogenic tic in ego development Psychoanalytic study of the child vol II 1946

7 Gromska J: Organic aspects in the etiology of motor neurosis in children. Polish medical journal 7:1247 1968

8. Harnack, G: Nervöse Verhaltensstörungen beim Schulkind Georg Thieme Stuttgart 1958

9 Holmborg P O and Billing L.: Tics: etiologi behandling och prognos Sv Läkartidn. 60:24 1963

10 Kanner L.: Child Psychiatry 3rd ed 1958 Thomas publ New York

11 Mahler Marg.: A psychoanalytic evaluation of tic in psychopathology of children Psychoanalytic study of the child vol III-IV 1949

12. Reich W: Der psychogene Tic als Onanieäquivalent Ztschr f Sexualwissenschaft 11:302 1925

13 Schachter M.: Tic oculaire simpl ou symptom localisé d une atteinte organique nerveuse centrale? Acta paedo-psychiatrica 29:40 1962

14 Torup E.: A follow-up study of children with tics Acta paediatrica 51:261 1962

15 Walton D: Experimental psychology and the treatment of tiquer J of child psychology 2 148 1961

16 Zausmer D.M.: The treatment of tics in childhood. Arch. Dis Child. 29 537 1954

CHAPTER XVIII

SYMPTOM CHANGES AND SYMPTOM LOAD

SYMPTOM CHANGES AND SYMPTOM LOAD

INTRODUCTION

A longitudinal study provides unique opportunities of following a variable flora of symptoms in the individual child over the years The limited task undertaken in the present study has been mainly concerned with the development of certain conspicuous symptoms which are easily observed by the mother It is the occurrence of symptoms of this kind in a normal child sample and the changes which they undergo as the children grow up that I have set out to describe

The first part of this essay deals with symptom changes The latter part with symptom load Previous chapters have described the persistence of various behavioural and developmental characteristics Changes in the longitudinally studied pure sample have been related to changes in cross-sectional figures The estimated percentage differences express the stability of the symptom.

The systematic review now in progress of practically all 4-year-old children in Sweden will presumably lead to the presentation of various statistical series concerning the children s physical and mental health. We should therefore try to analyse the implications of these figures before deciding whether they are satisfactory or disturbing Our assessment must allow for the extent to which the symptoms are transient or persistent

Method

The number of individuals represented in the diagrams below comprise a pure sample i e the diagrams reflect changes in children who attended every interview in the period 4-8 years. The only exception concerns a few children who have been included despit the fact that they were away for one of the five investigations in question. In these few cases the observation period has been 2 years instead of 1 year The pure sample numbers 198 cases

The diagrams depict (a) changes in cross-sectional frequenci s (b) persistence and (c) frequency of recurrences The linear graphs have been drawn to a logarithmic scale in order to bring out the mutual relative changes in frequency The number of case with the symptom in question at the age of 4 is shown on the left and the number at 8 years on the right Since the percentages refer consistently to the same number of children (198) the absolut and the percentage relationships shown by the right-hand scale corre pond to one another The lope of the line indicates a falling or a rising trend. Parall l line regardless of

their level denote the same relative change in symptom frequencies between 4 and 8 years

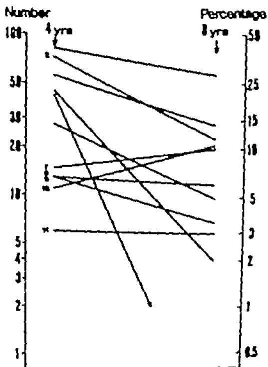
Cross-sectional frequencies at the different ages are given in Fig 1 while Fig 2-4 shows both the degree of persistence and the frequency of recurrences A persistent symptom is one that has been noted at each of the five investigations between 4 and 8 years; the frequency of recurrence denotes the number of cases in which the symptom reappeared at 8 years after it had been absent at one or several of the investigations between 4 and 8 years The triangular field between the graphs for persistence and recurrence provides some indication of the instability of the variable in question The data have been presented in separate figures purely for the sake of clarity

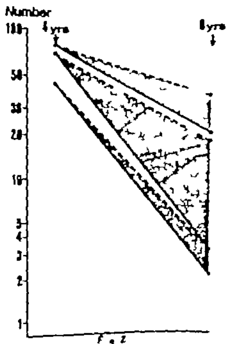
The frequency graduations of the variables used for these comparisons are those described most fully in the sections dealing with the various symptoms Estimates concerning non-nutritional sucking nailbiting tics and destructiveness are based on the established definite habit Two frequency gradings have been used for temper tantrums that in which the symptom is said to occur at least once a week and that in which it occurs daily Night waking has been included as symptomatic behaviour if it occurs at least once a week To be included in the estimate incomplete bladder and bowel control had to have been current at the time of the interview or to have occurred periodically during the observation year

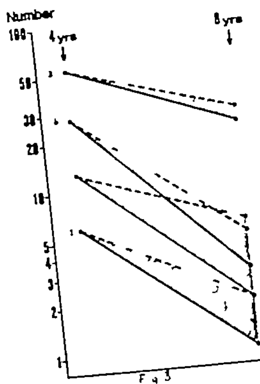
Results

Falling and rising trends in the occurrence of symptoms in the pure cross sectional sample at 4 and 8 years are illustrated in fig 1 The relative weight of the symptom variable is indicated by its position on the y-axis The divergence between curves reflects differences in the changes - the greater the divergence the greater the change between 4 and 8 years

Figs 2-4 provide some indication of the stability of the symptoms in terms of the relationship between their persistence and their tendency to recur For some of the variables the number of children who had the symptom at 4 years is quite small and the estimated figures should be interpreted with this in mind See figs on next pages

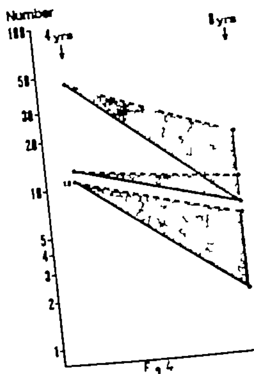

Number
Percentage
4 yrs
8 yrs
100
50
30
20
10
5
4
3
2
1
50
25
15
10
5
3
2
1
0.5
Fig 1


Number
4 yrs
8 yrs
100
50
30
20
10
5
4
3
2
1
Fig 2



Number
100
4 yrs
8 yrs
50
30
20
10
5
4
3
2
1

Fig 3



Number
100
4 yrs
8 yrs
50
30
20
10
5
4
3
2
1

Fig 4

Fig 1 Changes in cross-sectional frequencies between 4 and 8 years Pure sample Logarithmic scale

1 = night-awakening (weekly or more)
2 = temper tantrum (daily + several/week)
3 = non-nutritional sucking (def habit)
4 = destructiveness (def habit)
5 = temper (daily)
6 = night-wetting (nightly + periodically)
7 = stuttering (def habit)
8 = nailbiting ( )
9 = day-wetting (daily + periodically)
10 = tics (def habit)
11 = soiling (daily + periodically)

Fig 2. Changes in symptom frequencies of night-awakening (1) temper destructiveness (4), Pure sample Logarithmic scale

●———● = persistent number
●- - - -● = recurrent

Fig 3 Changes in symptom frequencies of non-nutritional sucking (3) night-wetting (6) day-wetting (9) soiling (11)

●———● = persistent number
●- - - -● = recurrent

Fig 4 Changes in symptom frequencies of disturbances in speech-flow (all grades) (7) nailbiting (8) tics (10)

●———● = persistent number
●- - - -● = recurrent

DISCUSSION

The analysis in this report is confined to ten symptom which can easily be observed by those around the child and whose degree and frequency could therefore be reported fairly reliably

Most of the symptoms described decline in frequency during the period (fig 1) Concern over the child s adjustment generally seems more pronounced at 4 years than after it has started school In several of the variables a proportion of the frequency comes from retarded or strikingly slow maturity: it is the tempo of development that deviates In these variables the symptoms at 4 years are a mixture of retarded development characteristics and secondary symptoms the latter consisting in a relapse into behaviour which is natural at an earlier age and does not differ from that which has occurred all the time This category includes deviations in the functional maturity of bladder and bowels temper tantrums destructiveness and perhaps non-nutritional sucking as well The steepest decline during the period is registered for daily outbursts of temper tantrums (see fig 1) and the habit of destructiveness In contrast to these symptoms there are those which do not occur until a later stage and which are still on the increase at 8 years These include tics nailbiting and to some extent stammering tendencies There is reason to suppose that these symptoms to a greater extent than the former category are expressive of emotional disturbances

As already noted, some problems are mainly age-conditioned so that they are widespread at certain ages By the time this stage has been passed they have lost a great deal of their intensity Development can be rapid and the picture may change within a few years It is hazardous to attach too much importance to the individual child s symptom for purposes of prediction but among all the children exhibiting symptoms of this kind there may be some in whom the symptom presages a serious disturbance It is important to be able to establish such a deviation from normality at an early stage to devise adequate criteria for appraising the content of the symptom. This would not appear to be possible in the case of an individual age-conditioned symptom.

Parents often entertain an ideal picture of how a child should behave any deviation being interpreted as pathological The occasion of their

perplexity may be the expression possibly exaggerated of a normal developmental characteristic This is particularly probable in the case of age-conditioned symptoms Behaviour is evaluated in terms of what it signifies and whether it occurs at a later age A patently age-conditioned symptom such as temper tantrums or destructiveness takes on a new significance at 7-8 years as compared with the corresponding symptom at 3-4 years Only the daily occurrence of temper tantrums at 6 years and subsequently deviates sufficiently from the behaviour of the group to warrant closer attention

Behavioural changes are sometimes temporary due to anxiety associated with a particular situation such as an accident a spell in hospital a tragedy in the family or a brief passing conflict in the home After a few months or a year a quieter period ensues and the symptom is no longer manifest Symptoms of this kind may have a good prognosis notwithstanding the drama which may accompany their inception Stammering that appears in chronological relation to an accident is no less likely to disappear than stammering due to other reasons Thus no reliable predictions can be made concerning acute situation-conditioned symptoms either

As can be seen from fig.2-4 symptom persistence varie considerably Some symptoms (e g thumb sucking) represent a persistent pattern which changes very slowly By 4 years the habit is of long standing and leaves no room for surprising changes Nailbiting a symptom at the developmental stage in these years persists in a high percentage of cases and recurs with a strikingly high frequency Other symptoms such as tics and stammering which are presumably under further development later on are more capricious and unpredi tabl For the most part these symptoms are so new during the bservation period covered here that they come and go Day- and nightwetting should also be included in the group of symptoms which are non-predictable at 4 years This is all the more apparent when the lement of deficient maturity has been reduced. The number of children with encopresis is too small to permit an interpretation of the curve

SYMPTOM LOAD

INTRODUCTION

As pointed out above the individual symptom cannot carry more than a limited prognostic value Findings at 4 years are repeated for only some children at the age of 8 Deviant behaviour of the kinds considered here thus occurs frequently at a certain age without being a sign of persistent disturbances

But even if an isolated symptom at 4 years is frequently short-lived it seems worth investigating whether children who present several overt behavioural disturbances at that age do so later as well

Another hypothesis to be tested is whether symptom load co-varies with intelligence Observations along these lines have been reported namely that psychic morbidity is more common among former members of special school classes than it is among others (6) and that the number of problem children in a normal sample diminishes as I Q. rises (2)

Children s symptoms of maladjustment are sometimes blamed on mothers who go out to work and are regularly absent from the home Data have accordingly been analysed to test this with reference to the ten symptoms considered here

Method

With a view to testing the above a chart of symptoms comprising the ten forms a deviant behaviour mentioned previously was compiled for the children at 4 and 8 years of age Each of the 198 children has been accorded a score for each variable 0 denoting that the symptom has not occurred 1 that it has been observed but only occasionally and 2 that it has been present to a marked degree This simplified grading has been used for the sake of uniformity even if the observations of intensity would have permitted greater differentiation. Symptoms that occur daily" every week" "usually" and often have all been rated as 2

In this way each child has been loaded with a score between 0 and 20 at the ages of 4 and 8 A nine-fold table comprising all the individuals has been constructed to compare children with low medium and high symptom loads at the two ages Separate calculations have been made for each sex.

To test the co-variation with intelligence an analysis has been made of the symptom loads carried by children in the extreme groups: high

I (120 or more) and low I Q. (80 or less) using the standardised Terman-Merrill quotients at 5 and 8 years respectively

Information on the mothers gainful employment up to the children s 3rd birthday has been taken from form O (longitud) item 70 The mothers who had full or half-time employment at every investigation formed one group in the comparison the other group comprising the mothers who never had gainful employment during this period The remaining mothers in the sample had been registered as working on some occasion or else the information was incomplete; these two categories were consequently excluded from the calculations

Results

The mean symptom scores were as follows:

Girls at 4 years	6 ± 2 2
at 8 years	5 9 ± 2 3
Boys at 4 years	5 9 ± 2 2
at 8 years	5 1 ± 2 2

In comparisons between 4 and 8 years X^2 values were as follows:

Girls	21 170	p = 001 (4 df)
Boys	23 101	p = 001 (4 df)

There is thus a statistically significant probability of a child having a high score at 8 years if it has a high score at 4 The children who are relatively free of symptoms in the variables investigated here at 4 years have a better chance than those with a high symptom load of also belonging to the low scorers at 8 years The number of deviant symptoms is thus of predicative interest

The comparison between symptom loads (3 levels) and the extreme groups as regards intelligence at 5 and 8 years of age resulted in the following table:

Table 1. Intelligence and symptom scores

	Symptom scores					
	At 4 years			At 8 years		
	0-4	5-6	7-13	0-3	4 5	6-13
I.Q. of 120 or more	7	6	7	9	8	2
I.Q. of 80 or less	4	2	11	3	6	8

The distribution in the sixfold table suggests particularly at 8 years of age that the least intelligent are those with the highest sympton load The differences in the present material are too small however to be statistically reliable (p = 20 resp 10 in X^2 values with Yates correction)

Data on the possibility of a connection between gainful employment by the mother when the child was very young and the sympton load of the child at 4 and 8 years are presented in Table 2

Table 2 Mothers gainful employment in relation to their children s sympton loads

	No of symptoms at 4 yrs		No of symptoms at 8 yrs	
	Average or more	Less than average	Average or more	Less than average
Part or full-time work at every investigation (1-3 yrs)	15	11	10	16
Never any gainful employment (1-3 yrs)	7/	38	54	58

Children whose mothers were orking full or part-time at every investigation between 1 and 3 years were not more loaded with symptoms at either 4 or 8 years of age than children whose mothers had never had gainful employment No co-variation could be demonstrated that might indicate a relationship

DISCUSSION

Many of the symptoms investigated here have been only temporary This possible runs counter to other reports in which the development of symptoms has been mapped in clinical cases To some extent at least the contradiction is more apparent than real The populations studied have varied in their composition. When changes in symptoms are studied on the basis of clinical cases after various methods have been used in the treatment of say stammering tics or sleep disturbances the sympton will usually have ex sted for a considerable time already and may even

have become fixed as an inaccessible neurotic symptom. The stability of the deviation will then differ from the stability in a sample of normal children where even the earliest manifestations of a deviation will be noted The instability in the development of the individual symptoms in the present sample is in keeping with the statement of Macfarlane et al (5) in their longitudinal study that the magnitude of interage correlations of problems suggests a nonpersistence over a long age span Similarly others have pointed out that early deviations are agebound phenomenon (4) or moderate predictors (3)

It is hardly surprising that a child with a large number of deviations at 4 years should be likely to have a large number at the age of 8 The variables in the analysis include some which have been shown to disappear slowly To some extent the symptoms of the other variables tested also persist between 4 and 8 years though only on a small scale But it is worth considering the predicative content in the amount (number) of deviant symptoms in the 4-year-old It is a sign that the lack of balance in the child s adjustment is more than temporary

Perhaps there is an element of stability in a propensity to react a flexible readiness to meet new situations (8 9) Each child makes individual attempts to find methods and develop a system for its adjustment to the internal and external environment There will be a risk of persistent symptoms insofar as this environmental pressure persists But since the family situation and childhood conditions change environmental pressure will vary and with it the child s reactions Clarizio (1) having reviewed various follow-up studies and retrospective studie published in recent years expresses his doubt as to a connection between early childhood maladjustment and later specific disability as follows: it would seem that change appears to characterize the course of behaviour deviations in children in as much as or more than, chronicity or stability" It is only when the results of longitudinal growth studies have been published from several quarters that the question can be given a more substantial answer

I am well aware that the behavioural variables chosen yield a limited picture of the child personality At this stage in the analysis of data my ambition has been to investigate the stability of and o

in the observations which the mothers have been able to report in a quantifiable manner concerning the children s behaviour Such information is an important but insufficient contribution to a full understanding the child s adjustment at these ages The symptoms may constitute a cry for help or a danger signal that flashes occasionally or more persistently They may be a reaction to a stress situation a defence that can also be interpreted as a healthy psychic reaction to an unsuitable internal or external strain They may represent a personal trait that is taken for a patholog cal sign. The concept of mental health and disease cannot be caught solely with the observable symptoms in the variables used or in other superficial variables.

Eventually a certain number of children will crystallize out from this normal child sample children whose previous data can be traced back in the wisdom of retrospect with a view to identifying the origins and causes of deviations in the development of their character and personality It will then be possible to evaluate the symptoms in a more balanced overall perspective This perspective as mentioned above will include personality tests and analyses of interaction with the environment the interpretation of which must be left to a future study

Summary and conclusions

Changes in the frequency of ten symptom variables have been followed in 198 children in the longitudinal Stockholm study by means of annual interviews between the ages of 4 and 8 years The following symptoms have been studied: night waking temper tantrums destructiveness finger sucking nailbiting tics stammering day wetting bedwetting and encopresis During these years notable changes occur in the symptom patterns of individual children. This is particularly the case with age-conditioned symptoms such as temper tantrums and destructiveness which become far less widespread by 8 years Symptoms diminish in other variables too with the exception of tics stammering and nail biting During the age period under consideration the latter three symptoms are of a more episodic and recurrent character than is e g finger sucking which is the most stable of all the symptoms

The symptom load in the above variables has been determined for every child at 4 years and at 8 years and a comparison has been made between the groups with the greatest and smallest loads It is not generally feasible to predict subsequent symptom developments on the strength of an isolated symptom in a 4 year-old If on the other hand the behavioural deviation is manifest in symptoms from several sectors of the 4-year-old s everyday life there is a far more patent risk of difficulties also occurring at 8 years

The accumulation of symptoms has been analysed in children belonging to extreme groups with respect to intelligence The distribution indicates a tendency for the least intelligent to have the greatest symptom load but the difference is no sufficiently great to rule out chance

The mothers who had regular employment when their child was 1-3 years old could not be shown to have a higher proportion of children with heavy symptom loads at children at 4 and 8 years of age than the mothers who never went out to work at that time

REFERENCES

1 Clarizio H.: Stability of deviant behaviour through time J Abnorm. Psychology 74: 288 1968

2 Jonsson G and Kälvesten A-L.: 222 Stockholmspojkar Summary in English. Monografier utgivna av Stockholms kommunalförvaltning Stockholm 1964

3 Kagan J and Moss H A.: Birth to maturity: study in psychological development New York Wiley 1962

4 Lapouse R, and Monk M.: American Journal of Orthopsychiatry 34: 436 1964

5 Macfarlane J Allen L. and Honzik M.: A developmental study of the behaviour problems of normal children between twenty-one months and fourteen years Berkeley Calif University of California Press 1954

6 Ramer T: The prognosis of mentally retarded children. Acta psych. et neurolog 1946 suppl 41

7 Robbins L: Deviant children grown up Baltimore Williams and Wilkins 1966

8 Rutter M. Birch H Thomas A. and Chess S: Temperamental characteristics in infancy and the later development of behavioural disorders British Journal of Psychiatry 110: 651 1964

9 Thomas A. et al: A longitudinal study of primary reaction patterns in children Comprehensive Psychiatry 1: 103 1960

CHAPTER XVIII

G E N E R A L   S U M M A R Y

GENERAL SUMMARY

This study is part of a longitudinal prospective investigation of the growth and behavioural development of upwards of 200 children from Solna-Stockholm which has been in progress since 1955 The Stockholm study is part of a major international project sponsored by the Centre International de l'Enfance in Paris Similar investigations are being conducted in London Paris Brussels and Zürich and with regard to certain ages, in two African centres namely Kampala and Dakar Although the ultimate aim of the project is to elucidate the influence of different international cultural environments upon the physical and mental growth of children each research group has been confronted by the initial task of carrying out a preliminary analysis of the extremely comprehensive information systematically collected concerning the children in its own sample

Chapter I gives a list of papers comprising this thesis

Chapter II A longitudinal interdisciplinary study of this kind is a matter of teamwork. As a member of this team from the inception of the Swedish study the writer has participated in the planning of the investigation and participated in its current design. Interim results of the work of the study group have been presented in various quarters by different members of the team. A collective presentation of the Swedish project was published in Acta Paediatrica 1968 suppl 187 with studies of somatic mental and social changes during the first three years of the children s lives The essay in this supplement which I helped to prepare and design have been appended in reprint form to the present enlarged report covering the first eight years of the children s lives A summary of the content and results of these previously published essays is given in Chapters III and VIII This also includes summaries of two joint papers with contributions from all five European longitudinal CIE studies

Chapter IV Gen ral description of r thod, provides a tabulated account of the somatic mental and social information collected at different ages Most of the behavioural data on which the results presented here are based have been taken from structured interviews conducted by a psychologist Each of the three at some ages four inter-

view forms with mental data comprises 80 items Each item is provided with a variety of fixed alternative answers Certain variables contain up to ten different variations and gradings A consistent aim has been to secure actually observed behaviour if possible quantifiable and frequency-graded Interpretations and evaluations have been disregarded in as large extent as possible Expressions of temper and emotion have also been measured in terms of exemplified behaviour per day per week per month or more generally by expressions such as "usually" often sometimes seldom" or "never" The content of certain mental variables is naturally elusive

The development and intelligence tests used to elucidate relations to different behavioural variables have been Brunet-Lezine (up to and including 2 years) and Terman-Merrill (at 3 5 and 8 years) On the other hand the evaluation of the various personality tests is not yet complete Consequently these tests have not been used in the present study The child psychologist s assessment of the child in different fixed variables on a 5-point scale has been used to elucidate certain development characteristics The clinical findings of the pediatric specialist have also served as a background. Detailed social data have been collected annually and used for estimates of relations to mental data either as a condensed social score or as detailed particulars e g concerning housing conditions and the parents educational level

Chapter V deals with the losses to the sample occurring during the first eight years of observation. These comprise 12 cases (= 5 6 % of the original number) Six of these left the inve tigation because they moved far away one was killed in a road accident and the remaining five declined for various reasons to take any further part in the investigation Compared with other extensive longitudinal studies the loss is trikingly small

The loss is distributed between families with different social scores The resultant changes in the social and economic composition of the sample are negligible compared to the social improvements undergone by the families in 8 years The children born out of wedlock still constitute the same proportion of the sampl as before Nor has

the loss had any disproportionate effect on families whose mothers have a particular educational background.

Chapter VI provides a discussion on the advantages and disadvantages of prospective longitudinal investigations The cross-sectional investigation which is more commonly employed gives results more quickly costs less and is more easily made representative of the group of community it sets out to portray The loss of subjects in project which is inevitable and affects any continuous study of children over a period of several years is of no account in a cross-sectional investigation A longitudinal study must comprise a more limited number of subjects if the material is not to become too unwieldy No such limitation is necessary when the subjects are only to be investigated once A large and comprehensive material makes the statistical analysis more reliable and detailed.

But cross-sectional studies also entail certain obvious disadvantages The only possible way of elucidating the relations between previous events and subsequent processes in a child s life is to make a continuous study of the phenomenon to be followed. Parents memories are too selective and unreliable A prospective longitudinal approach is essential if the errors which have been found to exist in retrospective methods are to be avoided. The distance in time between observations must be relatively short and is one of the criteria of the reliability of a study Within reasonable limits unremitting observation is indispensable in evolving a model for the most reliable prediction possible concerning the development of a certain behavioural characteristic Given sufficient allround data, a continuous investigation from birth makes it possible to test theories concerning the causes of deviant behavioural development

A bodily measurement or a behavioural characteristic may be accomodated within the normal distribution limits in a cross-sectional investigation but the development of the individual child at the age in question may nonetheless deviate from the optimum development rate for which it is programmed. An assessment of growth and development should always be related to previous conditions and to a narrower time factor than usually is afforded by cross-sectional figures The results of

longitudinal studies of a representative number should therefore provide paediatricians or child psychologists with a more reliable frame of reference for prognostic development assessments

Chapter VII enumerates the methods used in the statistical analysis

The summary presented below comprises the analysis undertaken by the writer of limited portions of the collected material The extensive information provided by the data cards concerning the habits and behavioural characteristics of the children before they attained typical school age has been utilised to illustrate development during the pre-school years Particular interest has been devoted to the stability of the observed patterns of habits and the predictive value of the various symptoms A prominent place is given in the study to the interrelationships of different behavioural variables and their relation to environments of different kinds

Chapter IX on Non-nutritional sucking in ages from infancy up to 6 years of age deals with:

1. the frequency of finger sucking its stability and sex differences at different ages
2. its relation to feeding methods and the duration of mealtimes
3. its relation to different forms of behaviour in connection with feeding
4. the relation of prolonged finger sucking to emotional symptoms and social variables at the ages of 3-5 years
5. possible connections between finger sucking and malocclusion at 9-12 years and enunciation defects at 4-5 years
6. parental reactions to the sucking habit

Practically all children suck their fingers or comforters during the first six months of life There is a sharp fall in the frequency curve during the second half of the infancy period. After this period the number only declines slowly Finger sucking established at the end of the first year is strikingly stable Girls were significantly more prone to finger sucking than boys at [illegible]

There was no demonstrable significant covariation with feeding methods breast and bottle feeding made no difference The weaning age from all nutritive sucking the duration of the breast or bottle meal and the satisfaction it afforded were inversely related to the established habit of finger sucking to an extent which was more than coincidental The intensity of the sucking habit during the first sex months of life was of uncertain predictive value with regard to the fixation of the habit

The prolonged finger sucking group (= 5 years or more) was not particularly prone to stress symptoms or adjustment difficulties compared to the other children. The variables studied were: loss of appetite sleep speech fluency tics nailbiting the children s sensitivity liveliness and destructive tendencies On the other hand mothers *employed solely in the home had more persistent thumb-suckers* around them than mothers who had been gainfully employed during the first three years of the child s life (p = 01)

Thirteen per cent more children in the group with sucking habits had symptoms of malocclusion than in the group with minimal sucking or none at all The difference was not statistically probable but the trend was always the same even as regards special malocclusions The groups are too small to give any reliable statistical verdict Apart from this general tendency it was found that 6 of the children with prolonged thumb-sucking and 2 of the 9 most persistent dummy suckers were free from symptoms

Minor defects of enunciation were more common among thumb-suckers at 4-5 years than among other children (p = 01)

The mothers attitude to habitual finger sucking was generally very tolerant Intensive reactions to the habit were only noted in 5 % of the cases at the age of 5 years Mechanical countermeasures against thumb sucking were rare A considerable change has occurred in this respect during the past 20 years.

The results of the study do not provide any conclusive answers concerning the etiology of the occurrence and fixation of the habit either in terms of the theory of learning or other theories Some findings

but not all agree best with the theory of non-gratified instinctual needs The prolongation may be a learned behaviour

Chapter X. Nailbiting, deals with the age frequencies of nailbiting the persistence of the symptom and its co-variation with certain other behavioural variables The frequency of children biting their nails daily gradually increased during the pre-school years and had reached 5 % by the time they started school If nailbiting of less than daily intensity was also included the frequency of nailbiters at the same age was 40 % The sex difference at the ages of 5 and 6 years was significant at the 1 % and 5 % levels respectively with a frequency predominance by the girls

The symptom shows a clear tendency to recur even if it is more or less episodic during the observed years

No chronological connections could be established between the appearance of nailbiting and the cessation of thumb-sucking Nor was there any statistically significant relation between the rise in frequency at 7-8 years and the school start al hough the figures were significant at a level of almost 5 %. No covariation could be established with stammering tendencies tics tendencies temper tantrums or biting directed against other persons Of the variables tested, only exceptional defiance exhibited more than a random coincidence with nailbiting The covariation of defiance and nailbiting can corroborate the hypothesis that one of the initial causes of nailbiting at the pre-school stage is connected with inhibited aggression. Aggressive feelings which may not be expre sed freely are vented in thi way instead.

In contrast to biting directed against other persons habitual nail biting seldom prompted any strong parental reactions during the first 5 years Such efforts as were made to induce the hild to abandon the habit were not particularly successful Improvement and deteriorations were fairly evenly distributed.

The essay on Rhythmic movements in infancy and early childhood (Chapter XI) comprise a study of the tereotypes expressed in rocking (jactatio) and/or head banging This behaviour mostly began during

infancy when it was at least occasionally reported in more than half the children. None of the children in this series had begun later than 18 months Three per cent of the 200 children in the sample continued their rhythmic bedtime rocking without interruption at least until they reached school age

Head banging appeared as a habit associated with tiredness and as a symptom of emotional excitation Although despair and anger were the underlying and decisive emotion in the majority of cases there were also cases of children banging their heads to seek pleasure

The stereotypes of these kinds persisting at 3 years showed no statistical relation to habitual thumb sucking night waking or teeth grinding Nor did children sleeping in a room of their own exhibit more stereotypes than others

Even if head banging and rocking were prolonged habits and a disturbance to the child s surroundings almost all these cases have no more special symptom load than others When the bed rocking behaviour persists for an exceptional length of time it can be compared to a conditioned reflex for obtaining release and satisfaction.

Chapter III is entitled Expectation and re lity concerning toilet training A general account is given here of toilet training methods toge her with the point at which full control is achieved over bladder and bowels The chronological connection between the commencemen of training and functional control is studied together with the stability of the control thus achieved and the effect of coercion during toilet training The relation between the rhythm of the bowel functions during the first months of life and subsequent difficulties and conflicts during training is tested

The latter part of the essay is devoted to a description of the occurrence development and covariation of primary and secondary forms of enuresis diurna and nocturna and encopresis A test is made of mean ability differences between groups with different forms of functional instability

The following results may be mentioned:

1 The median age for the first attempt at training was 8.4 months for the girls and 9 months for the boys

2. The median age for the commencement of continuous training was 10.9 months for the girls and 13 8 months for the boys The difference between these median ages is statistically probably significant

3 Day dryness occurred at a median age of 26 2 months for the girls and 27 9 months for the boys Night dryness was achieved by the girls at a median age of 27 6 months and by the boys at a median age of 28 5 months None of these differences was statistically significant

Bowel control was achieved by the girls at a median age of 20 months and by the boys at a median age of 25 7 months The sex difference is significant at a level of 1 %.

4. Children who began their training at an early age (< 9 months) did not achieve steady day dryness sooner than other children. Disregarding lapses in training steady results were achieved on average 20 months after its commencement

5 Boys offered significantly greater resistance to training and their training had to be suspended more often. The peak was attained at 18 months when 25 % of the girls and 40 % of the boys who were undergoing training had had to suspend it

6 At the same time as the majority of mothers were sympathetic and flexible in their attitudes to the children s resistance no less than 23 % of the children in the sample had been regularly subjected to coercion at some point in their training between 1-3 years. Neither the mother s education gainful employment nor her previous experience of children accounted for any significant differences in the frequency with which coercion was used.

7 Functional control was not achieved more rapidly or with greater

certainty after the use of coercion. Children who were late and unstable were subjected to more coercion than those who became clean at an early stage

8 Children described during infancy as irregular in their bowel functions had a more problematic toilet training at the age of 2 years than those noted for regularity

9 Coercion during training was not matched by refusal to eat or a tendency to nervous twitches during the pre-school years Nor was it reflected by residual utterances of defiance after the conclusion of the training period. On the other hand there was covariation between coercive training and early speech impediments

10 The prediction of bedwetting day wetting and encopresis in the four-year-old child in terms of corresponding behaviour on the attainment of school age was uncertain.

11 No mean quotient differences according to Terman-Merrill could be established between day and night wetters respectively and other children. The few children with primary encopresis were of inferior ability to children with primary day wetting (significance 05)

Chapter XIII A prospective longitudinal view of early speech impediments in a normal child sample This study deals with defects of speech fluency (tendency to stammering) during the pre-school stage and enunciation defects as symptoms of delayed speech maturity or as isolated symptoms not connected with any previously known speech retardation.

1. Defects of speech fluency even in their more lenient and temporary forms occur more often in boys than in girls There is a definite statistically significant sex difference between 5-7 years Stammering" during the pre-school stage is often temporary and of a clearly episodic nature Many of the defects of speech fluency reported by mothers at 3-4 years are presumably due to the fact that

speech has not yet attained sufficient stability and fixed organization so that it is relatively easily disrupted by environmental influences during the development phase

A chronological connection with an accident or some other defined frightening experience was established in 11 cases Apart from these presumable causal connections a significance test did not reveal any greater tendency to stammering in other children who had suffered accidents or frights Speech defects arising in connection with a dramatic experience known to the mother did not on average last longer than those which begun independently of any such experience

Speech reactions exhibited a significant covariation with conflicts during toilet training simultaneously noted loss of appetite (in boys) nervous twitches (both sexes) masturbation (both sexes) daywetting shyness and temper tantrums (in girls) The first of these is interpreted causally the remainder as simultaneous reactions in different behavioural variables to emotional tension

No connection could be established with weaning difficulties finger sucking nailbiting bedwetting or encopresis nor with social status the mother s education or marital status (at the time of the child s birth) or the birth of a sibling

B Enunciation defects and speech maturity assessed by a psychologist on a structured 5-point scale at 3 and 5 years showed a significant (p = 01) sex difference at 3 years but not at 5 years The girls were superior the boys Half the hildren who spoke indistinctly at 3 years were still speaking in an childish manner when they started school with indi tinct enunciation and/or difficulties with particular sounds lisping being the commonest defect

Speech retardation was less common among children whose parents were in the habit of reading to them. The test concerned reading habits noted at 2 years and speech retardation noted at 3 years (significance 05)

Naturally enough, ignificant (p = 001) mean differences of ability

measured in normalized Terman-Merrill quotients at 3 years were established between speech-retarded children and others These differences however remained practically unaltered if the same children were compared again at 8 years Speech-retarded 3-year-old children, taken as a group are at a disadvantage compared with other children when they start school Although there were children with specific speech retardation whose measured test results improved considerably between 3 and 8 years the group exhibited a large element of general retardation

Chapter XIV Further studies of sleep behaviour (mainly 4-8 years) This study contains data concerning the number of hours children sleep on average their access to bedrooms of their own and the extent to which they sleep in their parents bedroom difficulties encountered in putting children to bed and night waking and sleep disturbances As regards the last-mentioned of these particular interest has been devoted to behaviour on waking together with the incidence of sleepwalking and nightmares

Average lengths of sleep together with standard deviations for different ages are graphic illustrated. The correlation between length of sleep in the same children at different ages between 4-8 years was far better than that between the ages under 3 years but the correlation coefficient did not exceed 50 for any of the ages compared

Only 10-15 % of the children had access to a bedroom of their own Generally they shared a room with a sibling or siblings but in some 25 % of the families the children were still sleeping with their parents at the age of 8 years All the children had sleeping places of their own yet a strikingly large proportion of them spent some part of the night in their parents beds By 8 years the percentage had fallen to 18 % There was a statistically probability that children in social group 3 spent part of the night in their parents beds more often than other children. The mother s gainful employment did not influence the frequency rate in either direction

Both night waking and bedtime resistance are characteristics often reported as persisting in the same children year after year but the

This persistence is elucidated in figures.

A distinction should be drawn between night waking and sleep disturbances if the latter are taken to mean that sleep is disrupted by an emotionally disturbed state At 4 and 5 years most of the children who wake during the night show no sign of fright or disturbance but rather a need of playful attention or of a visit to the toilet The majority of cases of night waking at these ages are assumed to be related more to physiological variations in the depth of sleep than to mental imbalance

This assumption must be qualified by the observation that certain environment variables above all the placing of the child in strange surroundings (hospital orphanage or with a non-relative) produces a relatively greater frequency of night waking than in children who have not had such an experience between 4-5 years (p = 02) A similar tendency exists at 4 years but is not significant (p = 10) Corresponding separation effects have previously in this study been established in children aged between 2-3 years

Persistent night waking and prolonged defects of speech fluency occurred simultaneously to a greater extent than could be ascribed to coincidence

The occurrence of sleepwalking and nightmares has been studied in children aged 6-8 years Both conditions are often a transitory phenomenon, Approximately every tenth child is reported as sleepwalking from time to time during the observation period, In those cases where the symptom appeared more frequently it showed a marked tendency to persist Sleepwalking occurred too often in the same children in conjunction with unpleasant dreams to be due to mere coincidence Since according to the EEG and EMG investigations reported in the literature sleepwalking never begins during dream leep this clearly statistically significant covariation is surprising Probably the same background factors that initiate sleepwalking have the effect on other occasions of imparting particularly frightening qualitie to dream 1

Chapter IV Temper tantrums and destructiveness A description is given of the occurrence and [illegible]istence of symptoms in these two variab-

les from 4 to 8 years of age Both symptoms are markedly age-conditioned Their frequency declines steadily once the 4-year mark has been passed. A co-variation at the 5 % level is demonstrated between the variables at 4 years but not for the less frequent form of the symptoms observed at 8 years The boys are reported to be more destructive than the girls (p = 02) No sex difference has been found in the propensity for temper tantrums The content of the variables is discussed

Chapter XVI Tics in statu nascendi The questions dealt with in this essay concern the occurrence of tic-like symptoms up to the age of 8 years and the persistence and development of the symptom. A test is also made of the hypothesis of the relation between the early occurrence (at 3-5 years) of affect-motoric unrest exceptional liveliness and temper tantrum on the one hand and on the other the occurrence of tic-like twitches between the ages of 6-8 years

The prospective longitudinal investigation procedure is particularly well-suited for such a study Even milder forms can be included in the picture At an early age the commonest form is the incipient tic symptom which has not yet rigidified into a persistent and well-defined symptom.

Since tics are regarded as a symptom of emotional tension they have also been tested for covariation with other deviational and reactive forms of behaviour such as sleepwalking stammering and nailbiting Masturbation has also been related to tic symptoms

One s abiding impression on examining the longitudinal symptom chart of the various tic children is that in most of them the symptom occurs during definite periods sometimes with one or more years between them There were isolated cases where tics could be established as permanent from the age of 2 years but even in these children the frequency intensity was said to vary during the intervals between the annual interviews Symptom frequency in the group rose considerably throughout the observation period Tic-like symptoms were commoner in the boys than in the girls (p = 05)

The group of children noted at 3-5 years for general and exceptional

...eameas exhibited tic like symptoms i e twitches localized to
...in muscle groups one or more years later to a greater extent
the group of more quiet children (p = 05) Alternatively one
...ay that the general "muscular language of the younger child in-
...es a greater risk of developing into an involuntary gesticula-
language in the older child.

...e same time it was noted that temper tantrums were not frequency-
...lated with simultaneous or subsequent tic symptoms This obser-
...n suggests the hypotheses that both temper tantrums and tics pro-
a vicarious outlet for a rise in emotional tension

...ovariation of the tic symptom with stammering and with sleep-
...ing at the ages of 6-8 years was significant at a level of at
...t 2 % Masturbation (in girls) also accompanied tics to a greater
...nt than can be due to coincidence This could not be established
the boys

...e were no demonstrable relations to the nailbiting symptom which
...robably of a different etiological nature Nailbiting is presumab-
...ore closely related to defiance reactions than tics which con-
... a more dominant element of anxiety and fear

...ter XVII Symptom changes and symptom load A graphic presenta-
... is made of the changes between 4 and 8 years of age in the
...urrence persistence and recurrence of the following ten variab-
in the "pure longitudinal sample night waking bedwetting day
...ting encopresis temper tantrums destructiveness disturbed speech
... tics finger sucking and nailbiting The changes are plotted on
...garithmic scale making it possible to compare the extent to which
...nges have occurred in different variables Some indication of the
...bility of symptoms can be derived from the values for the number
persistent and the number of recurrent symptoms The extreme cases
this respect are non-nutritive sucking and daily temper tantrums

...the light of the demonstrabl instability the prognosis is discus-
... for deviations from so called normal behaviour among these pre-
...ool children. Since the symptoms are noted when relatively fresh,
... change in the population studied also reflect temporary deviations

that are conditioned by age and situations Such cases are hardly likely to be caught in follow-up studies of clinical materials on which experience of the prognosis has often been based in the past One should therefore be cautious when evaluating the results of cross-sectional population studies

The individual symptoms followed up longitudinally have thus been found to have only a limited predictive power On the other hand an accumulation of deviations in the individual child at 4 years of age is followed to a large extent by a corresponding symptom load in the variables tested at the age of 8 The probability of this occurring is not attributable to chance (p = 001) The observation is discussed with reference to other studies

A comparison of symptom loads between extreme groups of children as regards intelligence indicates that the less intelligent had greater symptom loads at both 4 and 8 years of age but the difference was not sufficient ~~eat to rule out coincidence (p = 10)

The symptom load at 4 and 8 years in children whose mothers had had regular employment when the children were small (1-3 years old) proved to be the same as the symptom load in children whose mothers had never had gainful employment at that time

APPENDIX

The questionnaire forms that were used at ages up to 3 years have been reproduced on pages 142 - 170 in Child Development An international method of Study Modern Problems in Pediatrics Edited by Frank Falkner S Karger New York. The item numbers and digits correspond to the references given in the present work except that part I in the above publication corresponds to the form designated no V in the Swedish study part II to form VI and part III to form VII

Excerpts from the questionnaire form for ages 4-5 years are given below with the numbers used for reference in the main text; in the case of items and digits that are exactly the same reference is made to the above publication

The arrangement and numbering of the items was changed at 6 years. The relevant excerpts from the questionnaire forms at 6-8 years are therefore reproduced below

Form V at 4 - 5 years

Dig

V: item 14-30 = V: item 14-30 at 0-3 years

V: 67 Does he ever stutter or stammer?

nil	0
occasionally	8
often	9

V: 68 Is there any difficulty with his talking?

nil	0
often	1
talks too much	2
bad accent	3
swearing	4
lisping/lalling	5
babyish	6
stuttering	7
difficult to understand	8
backward	9

Form VI at 4 - 5 years

VI: item	11-21	= VI: item	11-21	vid 0-3 years	
VI: "	24-29	= VI: "	24-29	"	
VI:	38-40	= VI:	38-40		
VI:	42-46	= VI:	42-46		
VI:	47-50	= VI:	47-50		
VI:	52-59	= VI:	52-59		
VI: "	61-72	= VI: "	61-72	"	"
VI:	75-76	= VI:	75-76		

VI: 77 Does he ever sleep in your bed?

never	0
less	1
odd periods	2
1 m or more: 1-2/w formerly	3
1-2/w still	4
sev/w formerly	5
sev/w still	6
nightly formerly	7
nightly still	8
always	9

[illegible] VII at 4 - 5 years

VII: item 57: 7 8 9 = VII: item 55 at 3 years

VII: 54 Does he often get into a tantrum? (Really marked temper)

never	0
mild temper only	3
less	4
1 or 2/week	5
sev /week	6
1 or 2 daily	7
several daily	8
many/day	9

		Dig
VII: item 55	How shown?	
	none of these	0
	lies on floor	2
	stamps	3
	slams doors	4
	hits inanimate objects	5
	hits people	6
	shouts	7
	throws things	8
	abuses M or F	9
VII: item 56	How shown? (continue)	
	screams	11
	bites	1
	rigid	2
	thrashing limbs	3
	pinches	4
	scratches	5
	hits	6
	hurts self	7
	blue in face	8
	other	9
VII: item 57	Parents reaction?	
	smack	11
	(never angry)	0
	other punishment (specify)	1
	reproach	2
	ignore	3
	laugh	4
	divert attention	5
	give own way	6
	comfort	7
	isolate	8
	other	9

VII: item 58-59 at 4-5 years — VII: item 58-59 at 3 years

VII: 75	Is he lively or quiet?	
	unquiet	4
	lively	5
	rather lively	6
	medium	7
	rather quiet	8
	quiet	9

Fo m V at 6 – 8 years

	never	rarely	some-times	often (or for 2 months)	always
Feeding					

Sleeping					
Item 16 Has he made a big fuss about having to go to bed?	0	1	2	3	4
Item 21 Has he ever wakened in t night? (after you have gone to bed)?	0	1	2	3	4
Item 22 Has he ever had bad dreams?	0	1	2	3	4
Item 23 Has he ever walked in his sleep?	0	1	2	3	4

Toilet	never	rarely	some-times	several times a week for 2 months or more	always
Item 24 In the daytime has he soiled? (lost bowel control)?	0	1	2	3	4
Item 25. At night time has he soiled? (lost bowel control)?	0	1	2	3	4
Item 26 In the daytime has he wet himself (lost bladder control)?	0	1	2	3	4
Item 27 At night time has he wet himself (lost bladder control)?	0	1	2	3	4

Habit	never	rarely	some-times	1 or 2 a day (for 2 months or more	several times a day
Item 32. Has he sucked his thumb or fingers	0	1	2	3	4
Item 33 Has he done any nail-biting?	0	1	2	3	4
Item 36 Have you seen him holding or playing with his privates?	0	1	2	3	4
Item 37 Have you seen any twitching blinking tics or other "nervous movements	0	1	2	3	4

Fears

----

	never	rarely	some- times	often (or for 2 months or more)	always
6 Has he stuttered or red?	0	1	2	3	4
17 Has he often had diffi- in getting words out?	0	1	2	3	4

bere some sounds which he t say properly?

al behaviour

- -

50 Is he often defiant when oted	0	1	2	3	4
57 Does he break things on oes?	0	1	2	3	4
60 Is he sometimes timid other children?	0	1	2	3	4

	never	less	1 or 2 a week	several times a week	daily or more
n 62 How often does he get o a real tantrum? (uncontrol- ble rage - not ordinary little pers)	0	1	2	3	4

- - -

an 66 Sleeping time?

	Dig
no investigation	0
less	1
7 hours	2
8	3
9	4
10	5
11	6
12	7
13	8
more than 13 hours	9

		Dig
Item 67	Bedtime?	
	no investigation	0
	at 6 p m or earlier	1
	7	2
	7 30 p m.	3
	8	4
	8 30	5
	9	6
	9 30	7
	10	8
	11 or later	9
Item 68	Awakening time?	
	no investigation	0
	at 4 p m. or earlier	1
	5	2
	5 30 p m.	3
	6	4
	6 30	5
	7	6
	7 30	7
	8	8
	9 or later	9
Item 69	Does the child sleep in parent s bed?	
	no investigation	0
	in P:s bed never	1
	seldom	2
	sometimes	3
	often	4
	in M:s bed never	5
	seldom	6
	sometimes	7
	often	8
	always	9

Social form (O) is the same as published in the abovementioned Modern problems in pediatrics A special condensed form (long comprising social data from the first 3 yrs has been made Thi is given below

C born in year	item 11	
month	12	
Mother s age at C s birth yrs	13	14
Father s	15	16
Time relation marriage/C s birth	17	
Completeness of family during C s first 3 yrs	18	
Residency when C 3 yrs	19	
M:s occupational status during C s first 3 yrs	20	
C s birth order among living born siblings	21	
C s order among siblings at home at birth	22	

	When C is	1 yr	2 yrs	3 yrs
Number of children at home	item	23	42	61
Number and sex of older siblings at home or fosterhome		24	43	62
Number and sex of younger siblings at home or fosterhome		25	44	63
Swedish social classification		26	45	64
Graffar system:				
Occupation British (M s highest)		27	46	65
Occupation modified ( )		28	47	66
Education		29	48	67
Sources of revenue		30	49	68
Income grouping		31	50	69
Dwelling		32	51	70
Total scoring original		33-34	52-53	71-72
Total classification original		35	54	73
Total scoring modified		36-37	55-56	74-75
Global classification modified		38	57	76
Income magnitude in 100 krs		39-41	58-60	77-79
M s education when C 3 yrs				80

Some used code for Social form (long.), sum for the first 3 years

C born in month

Dec	12	12
Nov	11	
Oct	0	
Jan	1	
Febr	2	
Sept	9	

Time relation marriage/C:s birth

unmarried	0	11
within 1-8 months after marriage	1	
" 9-23	2	
3 rd year of marriage	3	
4 th	4	
5 th	5	
6 th	6	

Completeness of family during C:s first 3 years

in fosterhome at 3 yrs	12	18
at C:s birth: M married F later divorced and later married another man	11	
M married F not divorced	1	
M later separated	2	
M later divorced	3	
M unmarried living with F later married F	4	
M unmarried living with F continuously	5	
M unmarried living with F later separated	6	
M unmarried living single continuously	7	
M unmarried living later on with another man	8	
M unmarried married later on another man	9	

Residency, when C 3 yrs

living in Solna	1	19
in Stockholm and inner suburban area (not Solna)	2	
in outer suburban area of Stockholm	3	
outside of Greater Stockholm in town	4	
in rural	5	

M:s occupational status during C:s first 3 yrs

information lacking for any of the three investigations	12	20
full-time occupation at each investigation	1	
full-time or part-time occ at each investigation	2	
never any occupational work	3	
rest (= did occupational work on some occasion)	4	

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

161 Palmrose, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965

162. Lundmark, Karl Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966

163. *Newborn Infant Cry*. Edited by John Lind. Sw. kr. 30.— 1965

164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 25.— 1966

165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shaw, J. H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966

166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966

167. Franzén, Torbon, Leucaemia in Infancy and Childhood. A Material of 378 Danish Cases. Sw. kr. 30.— 1966

168. Treiberth, W. Fetal Spot Discharges in Children. Longitudinal Study. Sw. kr. 25.— 1966

169. Dahl, Matti, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966

170. Bellman, Magnus, *Studies on Encopresis*. Sw. kr. 30.— 1966

171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 20.— 1966

172. *Festschrift in Memory of Constantin Chevrolat*. Sw. kr. 35.— 1967

173. Walsh, E. Zoe, The Esophageal Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967

174. Petersson, Per Olov, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967

175. Hiltunen, Pentti, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967

176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967

177. *Proceedings of the Fifteenth Northern Pediatric Congress*, Bergen, 1967. Sw. kr. 35.— 1967

178. Ackerot, Irène, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967

179. *Quantitative Studies of the Human Neonatal Circulation*. Edited by Göran Wallgren. Sw. kr. 25.— 1967

180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using Passive Haemagglutination Technique. Sw. kr. 20.— 1968

181. Koch, Göran, *Lung Function and Acid-Base Balance in the Newborn Infant*. Sw. kr. 20.— 1968

182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968

183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968

184. [illegible] Bengt, The intrapulmonary arterial pattern in normal and in transposition of the great arteries. Sw. kr. 25.— 1968

185. Andersen, Ebe, Skeletal Maturation of Danish School Children in Relation to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968

186. Dunn, Henry G., The Prader-Labhart-Willi Syndrome: Review of the Literature and Report of Nine Cases. Sw. kr. 25.— 1968

187. Karlberg, Petter, et al., The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1969

188. Mossberg, Gunnar W. and Mohn, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969

189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969

190. Hembäck, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969

191. Korvikko, Aarni, Cardiovascular Responses of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969

192. Väänänen, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 25.— 1969

193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969

194. Emanuelsson, Agnes, Studies on the Serum Binding of Vitamin B₁₂ in the Newborn Human Infant. Sw. kr. 30.— 1969

195. Thorn, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 25.— 1969

196. Rosberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969

197 Saxén, Ritva, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 20.— 1969

198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969

199. Villmann, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969

200. Sexton, Dina M., Cravioto, Joaquín, Rosales, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970

201. Sutherland, Lynette E., Hartroft, Phyllis, Balis, John U., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970

202. Fomon, Samuel J., Filer Jr., L. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970

203. Aarskog, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970

204. Berg, Kristian, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970

205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970

206. *Proceedings of the Eleventh Scandinavian Paediatric Congress*, Turku, August 2–August 5, 1970. Edited by Matti Dahl. Sw. kr. 35.— 1970

207 Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 25.— 1970

208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970

209. Rane, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on *Primary School Children in Umeå*. Sw. kr. 35.— 1970

210. Rosberg, Georg, Parental Attendance in Pediatric Hospital Admissions. Sw. kr. 25.— 1971

211. Eriksson, Margareta, Salicylate-induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971

212. Helminen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971

213. Landtman, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971

214. Samuelson, Göran, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 25.— 1971

215. Bergsman, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped Children. Sw. kr. 25.— 1971

216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971

217 *Pediatric Work Physiology, Proceedings of the Karolinska Institutet Symposium, Stockholm, August 30–September 1, 1970.* Edited by Claes Thorén. Sw. kr. 35.— 1971

218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 35.— 1971

219. Jaffé, Doris, Hartroft, Stanley, Manning, Mary and Eleta, Graciela, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. Sw. kr. 25.— 1971

220. Holmen, Paula, Backström, Leena, Kantero, Raija-Liisa and Tiisala, Ritva, Studies on Growth of Finnish Children from Birth to Ten Years. Sw. kr. 30.— 1971

221. Bohman, Michael, A Comparative Study of Adopted Children, Foster Children and Children in Their Biological Environment Born after Undesired Pregnancies. Sw. kr. 25.— 1971

222. Johansson, Erkki, Plasma Magnesium Levels during the First Five Days of Life. Sw. kr. 30.— 1971

223. Fomon, Samuel J., Thomas, Lora N., Filer Jr., L. J., Ziegler, Ekhard E., and Leonard-Michael T. Food Consumption and Growth of Normal Infants Fed Milk-based Formulas. Sw. kr. 25.— 1971

224. Klackenberg, Gunnar, A Prospective Longitudinal Study of Children. Data on Psychic Health and Development up to 8 Years of Age. Sw. kr. 35.— 1971

Price Swed. kr 30.—

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

TRYCK

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 225 1971

PHYSICAL GROWTH OF CHILDREN WITH CONGENITAL HEART DISEASE

PRE- AND POSTOPERATIVE STUDY OF 355 CASES

BY PIRKKO SUONINEN

ALMQVIST & WIKSELL PERIODICAL COMPANY STO

List of Supplements to Acta Pædiatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksells Boktryckeri AB, Uppsala, Sweden without charge.)

161. Palmeen, T. and Hirvonen, L., Experimental Studies on Fetal and Neonatal Circulation. Sw. kr. 20.— 1965
162. Lundeack, Axel Martin, Bone Marrow Cell Proliferation in Health and in Haematological Disease during Childhood. Sw. kr. 25.— 1966
163. *Newborn Infant Cry.* Edited by John Lind. Sw. kr. 30.— 1965
164. Böttiger, Margareta, Studies on Immunization with Inactivated and Live Poliovirus Vaccines. Sw. kr. 20.— 1966
165. Glauser, E. M., Cook, C. D., Harris, G. B. C. and Shwachman, H., Bronchiectasis: A Review of 187 Cases in Children with Follow-up Pulmonary Function Studies in 58. Sw. kr. 20.— 1966
166. Laaksonen, Anna-Liisa, A Prognostic Study of Juvenile Rheumatoid Arthritis. Analysis of 544 Cases. Sw. kr. 35.— 1966
167. Iversen, Torben, Leukaemia in Infancy and Childhood. A Material of 570 Danish Cases. Sw. kr. 30.— 1966
168. Trojaborg, W., Focal Spike Discharges in Children. A Longitudinal Study. Sw. kr. 35.— 1966
169. Dahl, Mauri, Intracardiac Phonocardiography of the Right Heart in Children. Sw. kr. 30.— 1966
170. Bellman, Margot, Studies on Encopresis. Sw. kr. 30.— 1966
171. Olding, Lars, Bacterial Infection in Cases of Perinatal Death. A morphological and bacteriological study based on 264 autopsies. Sw. kr. 20.— 1966
172. *Festschrift in Memory of Constantin Chermak.* Sw. kr. 35.— 1967
173. Walsh, S. Zoe, The Electrocardiogram during the First Week of Life. Sw. kr. 15.— 1967
174. Petersen, Per Ove, Atrial Septal Defect of Secundum type. A clinical study before and after operation with special reference to haemodynamic function. Sw. kr. 25.— 1967
175. Hansson, Folke, Vectorcardiographic Studies in Newborn Infants. Sw. kr. 25.— 1967
176. Berglund, Bo, Studies on Respiratory Syncytial Virus Infection. Sw. kr. 20.— 1967
177. *Proceedings of the Fifteenth Northern Pediatric Congress, Bergen.* 1967. Sw. kr. 35.— 1967
178. Kjellman, Bengt, Echoencephalography in Paediatric Practice with Special Regard to Measurement of the Ventricular Size. Sw. kr. 25.— 1967
179. *Quantitative Studies of the Human Neonatal Circulation.* Edited by Göran Wallgren. Sw. kr. 25.— 1967
180. Andersen, Hans Jørgen, Clinical Studies on the Antibody Response to *E. Coli* O-Antigens in Infants and Children with Urinary Tract Infection, Using the Passive Haemagglutination Technique. Sw. kr. 20.— 1968
181. Koch, Gösta, Lung Function and Acid-Base Balance in the Newborn Infant. Sw. kr. 20.— 1968
182. Westphal, Otto, Human Growth Hormone. A Methodological and Clinical Study. Sw. kr. 25.— 1968
183. Robertson, Alex F. and Sprecher, Howard, A Review of Human Placental Lipid Metabolism and Transport. Sw. kr. 25.— 1968
184. Robertson, Bengt, The intrapulmonary arterial pattern in normal infancy and in transposition of the great arteries. Sw. kr. 25.—

Kim, Skeletal Maturation of Danish School Children to Height, Sexual Development, and Social Conditions. Sw. kr. 40.— 1968

G., The Prader-Labhart-Willi Syndrome: Review of Literature and Report of Nine Cases. Sw. kr. 25.— 1968

Karlberg, Petter, et al., The Development of Children in a Swedish Urban Community. A Prospective Longitudinal Study I–VI. Sw. kr. 30.— 1968

188. Mossberg, Gunnar W. and Melin, Kerstin, Studies in Glucose-Galactose Malabsorption. A Clinical Study of 6 Cases and Genetic Study. Sw. kr. 25.— 1969
189. Fällström, S. P., On the Endogenous Formation of Carbon Monoxide in Full-Term Newborn Infants. Sw. kr. 20.— 1969
190. Hörnblad, P. Yngve, Experimental Studies on Closure of the Ductus Arteriosus Utilizing Whole-Body Freezing. Sw. kr. 20.— 1969
191. Korvikko, Aarni, Cardiovascular Response of the Neonatal Lamb to Hypoxia, Hypercapnia and Metabolic Acidosis. Sw. kr. 30.— 1969
192. Vihma, Leena, Surveillance of Acute Viral Respiratory Diseases in Children. Sw. kr. 30.— 1969
193. Rantakallio, Paula, Risk Groups of Low Birth Weight and Perinatal Mortality. 1969
194. Kasanen, Arvo, Studies on the Serum Binding of Vitamin B12 in the Newborn Human Infant. Sw. kr. 30.— 1969
195. Thoren, Ingrid, Cerebral Symptoms in the Newborn. Sw. kr. 35.— 1969
196. Roseberg, Georg, Social and Psychological Factors Influencing Hospital Admission of Children. Sw. kr. 20.— 1969
197. Sandin, Bernt, Pseudomonas Infections in a Paediatric Surgical Unit. Sw. kr. 25.— 1969
198. Koski, Maija-Liisa, The Coping Processes in Childhood Diabetes. Sw. kr. 30.— 1969
199. Välimäki, Ilkka, Tape Recordings of the Electrocardiogram in Newborn Infants. Sw. kr. 30.— 1969
200. Saujes, Dina M., Chrismo, Joaquin, Ramires, Lydia and van Veen, André, Infant Feeding and Weaning Practices in a Rural Preindustrial Setting. A Sociocultural Approach. Sw. kr. 35.— 1970
201. Sutherland, Lynette E., Hartwell, Phyllis, Baker, John H., Bailey, John D. and Lynch, Matthew J., Bartter's Syndrome. A Report of Four Cases, Including Three in One Sibship, with Comparative Histologic Evaluation of the Juxtaglomerular Apparatuses and Glomeruli. Sw. kr. 30.— 1970
202. Fomon, Samuel J., Filer Jr. J., Thomas, Lora N., and Rogers, Ronald R., Growth and Serum Chemical Values of Normal Breastfed Infants. Sw. kr. 30.— 1970
203. Annerén, Dagfinn, Clinical and Cytogenetic Studies in Hypospadias. Sw. kr. 35.— 1970
204. Berg, Kristina, Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age. Effects of Physical Training and Improved Nutrition. Sw. kr. 35.— 1970
205. Zweymüller, Ernst and Preining, Othmar, The Insensible Water Loss of the Newborn Infant. Sw. kr. 30.— 1970
206. *Proceedings of the Sixteenth Scandinavian Paediatric Congress, Turku, August 2–August 5, 1970.* Edited by Matti Dahl. Sw. kr. 35.— 1970
207. Olsson, Torsten and Victorin, Lars, Transthoracic Impedance, with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs. Sw. kr. 35.— 1970
208. Eeg-Olofsson, Orvar, The Development of the Electroencephalogram in Normal Children and Adolescents from the Age of 1 through 21 Years. Sw. kr. 25.— 1970
209. Rune, Valdemar, Acute Head Injuries in Children. An Epidemiologic, Childpsychiatric and Electroencephalographic Study on Primary School Children in Umeå. Sw. kr. 35.— 1970
210. Roseberg, Georg, Parental Attitudes in Pediatric Hospital Admissions. Sw. kr. 25.— 1971
211. Eriksson, Margareta, Salicylate-Induced Foetal Damage Late in Pregnancy. An Experimental Study in Mice. Sw. kr. 25.— 1971
212. Hakulinen, Alpo, Urinary Excretion of Vanilmandelic Acid of Children in Normal and Certain Pathological Conditions. Sw. kr. 35.— 1971
213. Lundmark, Bernhard, Clinical and Morphological Studies in Congenital Heart Disease. A Review of 777 Cases. Sw. kr. 25.— 1971
214. Samuelson, Göran, An Epidemiological Study of Child Health and Nutrition in a Northern Swedish County. I. Food Consumption Survey. Sw. kr. 25.— 1971
215. Bergman, Sheila Margaret, A Study of the Mental Health of the Near Relatives of Twenty Multihandicapped Children. Sw. kr. 25.— 1971
216. Michelsson, Katarina, Cry Analyses of Symptomless Low Birth Weight Neonates and of Asphyxiated Newborn Infants. Sw. kr. 25.— 1971
217. *Pediatric Work Physiology. Proceedings of the Karolinska Institutet Symposium, Stockholm, August 30–September 1, 1970.* Edited by Claes Thorén. Sw. kr. 35.— 1971
218. Rantakallio, Paula, The Effect of a Northern Climate on Seasonality of Births and the Outcome of Pregnancies. Sw. kr. 35.— 1971
219. Jaffe, Doris, Hartroft, Stanley, Manning, Mary and Eleta, Gracela, Coronary Arteries in Newborn Children. Intimal Variations in Longitudinal Sections and Their Relationships to Clinical and Experimental Data. Sw. kr. 25.— 1971
220. Heimann, Nala, Bäckström, Leena, Kantero, Raija-Liisa and Tiisala, Riitta, Studies on Growth of Finnish Children from Birth to Ten Years. Sw. kr. 30.— 1971
221. Bohman, Michael, A Comparative Study of Adopted Children, Foster Children and Children in Their Biological Environment Born after Undesired Pregnancies. Sw. kr. 25.— 1971
222. Johansson, Erkki, Plasma Magnesium Levels during the First Five Days of Life. Sw. kr. 30.— 1971
223. Fomon, Samuel J., Thomas, Lora N., Filer, Jr., L. J., Ziegler, Ekhard E., and Leonard-Michael T., Food Consumption and Growth of Normal Infants Fed Milk-based Formulas. Sw. kr. 25.— 1971
224. Mackenberg, Gunnar, A Prospective Longitudinal Study of Children. Data on Psychic Health and Development up to 8 Years of Age. Sw. kr. 35.— 1971

Price Swed. kr 30.—

Cover printed in Sweden by Almqvist & Wiksells Boktryckeri AB, Uppsala

FROM THE CHILDREN'S HOSPITAL, UNIVERSITY OF
HELSINKI FINLAND

PHYSICAL GROWTH
OF CHILDREN WITH CONGENITAL HEART DISEASE

PRE- AND POSTOPERATIVE STUDY OF 355 CASES

BY
PIRKKO SUONINEN

ACADEMIC DISSERTATION

TO BE PUBLICLY DISCUSSED BY PERMISSION OF THE MEDICAL FACULTY OF THE UNIVERSITY OF HELSINKI IN THE AUDITORIUM OF THE CHILDREN'S HOSPITAL ON DECEMBER 17TH 1971 AT 12 NOON

HELSINKI 1971

Also to be published as Supplement No 225 of
Acta Paediatrica Scandinavica 1972

[illegible] ted [illegible] Finland
[illegible] Oy Lappeenranta

ACKNOWLEDGEMENTS

The subject for the present study was proposed by my respected teacher in paediatric cardiology Professor Bernhard Landtman, M.D head of the cardiac department of the Children s Hospital, University of Helsinki. Without his strong encouragement, generous advice and tactful persistence this report would not exist. For all this I am very grateful to him.

I wish express my thanks to my teacher of paediatrics, Professor Niilo Hallman, M.D., head of the Children s Hospital, University of Helsinki, who kindly placed the facilities of his hospital at my disposal.

My special thanks are due to my good friend and superior during several years, Docent Leena Tuuteri, M.D and to Docent Riitta-Liisa Kantero M.D who in spite of their many personal duties never refused to discuss problems or to give valuable advices.

I am greatly indebted for Docent Eric Ivar Wallgren, M.D who on reading the manuscript offered friendly criticism.

I am sincerely grateful to Professor Matti Sulamaa, M.D head of the surgical department of the Children s Hospital, and to his staff above all Docents Mikko Paula, M.D and Ilmo Louhimo M.D as also to Mr Toivo Suutarinen, M.D and his anaesthesiology staff without their respective activities this study would not have been possible.

Docent Per Erik Heikel, M.D., and his staff performed the roentgenological examinations, for which I express to them my best thanks.

Further I extend my thanks to Mr Jorma Torppa, M.Sc., and Mr Markku Korhonen, M.Sc., for carrying out the statistical analyses at the Computing Centre of the University of Helsinki.

It is a pleasure to me to express my warm thanks to the personnal of the cardiac department of the Children s Hospital, above all to Miss Eila Tormanen, who has always been ready to help me in many practical problems in the collection of the data, and to Mrs. Marjo Karppi for drawing the graphs.

Particular thanks are due to Miss Elvi Kaukokallio for her excellent co-operation in translating the manuscript into English.

The study was aided by a grant from the Paavo Nurmi Foundation and the Sigrid Jusélius Foundation in Helsinki.

Helsinki, September 1971

P.S

CONTENTS

INTRODUCTION 7

REVIEW OF THE LITERATURE 8

OBJECT OF THE INVESTIGATION 11

MATHERIAL AND METHODS 12

CLASSIFICATION OF DIAGNOSES AND SELECTION OF CASES FOR STUDY 12
- Patent ductus arteriosus (PDA) 12
- Patent ductus arteriosus with pulmonary hypertension (PDA + PH) 12
- Coarctation of the aorta (Co) 12
- Tetralogy of Fallot (TF) 12

METHODS OF STUDY 12
- Heredity pregnancy delivery birth weight, extracardiac congenital anomalies and age at diagnosis 12
- Height and weight measurements 13
- Physical capacity 13
- Predisposition to infectious diseases 13
- Auscultation 13
- Congestive heart failure 13
- Blood pressure 13
- Laboratory tests results 13
- Interpretation of electrocardiograms 13
- Heart size measured from roentgenograms 14
- Surgical techniques and complications 14
- Surgical mortality 15
- Statistical analysis of the results 15

RESULTS 16

PATENT DUCTUS ARTERIOSUS (PDA) 16
- Boys 16
- Girls 17
- Comparison between boys and girls 19
- Correlations between the various factors 19
- Summary f results in the ncomplicated PDA group 19
- Discussion 21

PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION (PDA PH) 22
- Boys 22
- Girls 23
- Comparison between boys and girls 25
- Correlations between the various factors 26
- Summary of results in the PDA + PH group 26
- Discussion 26

COARCTATION OF THE AORTA (CO) 29
Boys 29
Girls 31
Comparison between boys and girls 33
Correlations between the various factors 33
Summary of results in the coarctation group 35
Discussion 35
TETRALOGY OF FALLOT (TF) 36
Boys 36
Girls 38
Comparison between boys and girls 40
Correlations between the various factors 40
Summary of results in the TF group 40
Discussion 42
GENERAL DISCUSSION AND CONCLUSIONS 43
REFERENCES 46

Introduction

Society sets for the individual various patterns which he must fulfil in order to be considered normal In childhood one of the requirements that can be most clearly followed is good physical development.

The first information that we have on child growth are the measurements made by Count de Montbeillard in France of his son from birth in 1759 up to 1777 (149) His measurements were carried out carefully and compare well even with present-day measurements.

Actual scientific measurements on the course of physical growth begin t be available in the nineteenth century when Quetelet in 1871 published in Belgium (138) the studies which he had begun already some 30 years earlier Since then, studies of height and weight growth have been published in different parts of the world with the aid of which the influence of hereditary racial, climatic social and other factors has been clarified in part at least

In Finnland a group of investigators, the Finnish Centre for Study in Child Growth and Development, has investigated the height and weight growth of the Finnish child (12 162). The results of these studies were used as standards of normal development in the work described in the present report.

Retardation of growth is observable in all chronically ill children, most commonly in those affected with endocrinological and neurological disturbances, kidney lung, bone and digestive tract diseases, or cardiac and vascular diseases.

It is the aim of society to ensure the best possible normal physical development to every child regardless of any disease from which he may suffer In order that this aim can be achieved in the case of children with congenital heart disease we must know the various factors that influence physical development A desire to add to this knowledge m tivated the undertaking of the present investigation the object of which was to examine some factors that influence child growth in certain types of congenital heart disease.

Review of the literature

The past three decades have witnessed an extensive and fruitful activity in cardiological research, as has the whole twentieth century in the investigation of physical development.

Rapid progress in heart surgery began with the successful operation for a patent ductus arteriosus performed by Gross in 1938. Crafoord was the first to perform in 1944 surgery for coarctation of the aorta, soon thereafter followed by Gross. One of the most significant events in the treatment of congenital heart disease was, however, the palliative operation developed by Blalock and Taussig in 1944 for certain congenital heart diseases of the cyanotic group in which the blood flow to the lungs is decreased. After these advances progress continued to its present-day level.

Already before cardiac surgery was begun, an extensive study had been made on the incidence of and prognosis in congenital heart diseases (1). As surgical procedures became more common, study of the symptoms arising from congenital heart disease has gained new significance, even if problems relating to diagnosis, surgical techniques, anaesthesia and postoperative care have come to the forefront.

With the general adoption of heart surgery it has been possible to follow the progress of the patient both during conservative treatment and after either a palliative or a corrective operation according to the nature of the defect. This has enabled the clarification [illegible] to some extent of the effect of abnormal haemodynamics on the patient's physical development.

In 1959 Mar[illegible] (117) [illegible]timated that congenital heart defects are the second highest in frequency as a cause of retarded growth.

A number of reports have been published on studies working to determine the degree and incidence of growth retardation caused by congenital heart defects. Growth [illegible] has been defined in different ways [illegible] some of them [illegible] the 10th p[illegible] the 3rd and some [illegible] a [illegible] retarding [illegible] the criteria used [illegible]

Patent ductus arteriosus. The first patient with patent ductus arteriosus operated on by Gross was an underweight girl of 7 years (70) and his first ten patients included five who were retarded in growth. The operation had a favourable effect on growth in all of the four patients who survived of these five (66).

Also Crafoord's first surgical patient in Europe was a slender girl of 7 years (4[illegible]). Among his first twenty patients there were only two with definite retardation of physical development and some showed a moderate degree of retardation, but the majority varied within normal limits (43).

Numerous investigations have been made of the growth of patients with a patent ductus and it has generally been found to be retarded from the normal (4, 5, 10, 11, 39, 41, 50, 56, 57, 58, 61, 6[illegible], 71, 78, 91, 95, 97, 109, 116, 1[illegible]1, 137, 144, 154, 164, 166, 168, 169). The series studied range in size from 9 to 643 patients. In about a fourth of the patients, in some series in nearly a half, there was observed retardation of growth, which was defined in somewhat differing ways in the various studies and was not at all defined in some.

There also are studies in which growth retardation was moderate in a part of the series (111), growth disturbance was rare (103) or not more common than in the general child population (53) or was not found in any of the cases (18). These series consisted of 10-211 patients with patent ductus arteriosus.

The lag from the standard has been found to be greater with respect to weight than to height, the latter being within normal limits (58) or only slightly retarded (10) in series ranging from 6 to [illegible]3 patients. A group of 10 patients has also been published with the mean weight below normal and the mean height above normal ([illegible]). Potter (136) in 1947 was the first to call attention to retardation specifically in height by comparing three patients having height measurements within normal limits and their lower relations, and a definite difference was found between the patients and their relations. Height measurements are not included in all the studies published in the literature.

In studies in which the results are stated separately for boys and girls, growth retardation has been found to be more marked in boys than in girls (95 106).

Following surgery definite acceleration of growth was observed in nearly all the studies. Even patients whose weight preoperatively was within normal limits were found to accelerate postoperatively in weight growth (11 155) or in both height and weight growth (50) The age at operation for a patent duct s has been found to have some influence on postoperative growth. The latter has been observed to accelerate more rapidly in patients operated on when under 3 years of age (56 107 121) under 5 years (50) or generally at an early age (5) There also are series in which the age at operation had no effect on the postoperative height and weight growth in patients who underwent surgery before the age of 8 years (169) or before the age of puberty (58)

Although a definite acceleration of both height and weight growth was observed after operation, an unexpectedly large proportion of the children remained permanently below the standard for normal (5 41 56 109 144 169). This was ascribed to the age at operation, the age of 4 5 years already being considered too late in these cases (56) or to some prenatal factor on which haemodynamics had no influence (169).

Patients with a patent ductus arteriosus may thus be retarded in growth. As early as in 1939 growth disturbance was considered to be an indication for operation (79) It was in fact one f the first generally accepted indications in the early days of ductus surgery

A low birth weight and the presence of xtracardiac congenital defects have been f und to have a negative influence on the growth of children w th patent ductus (168) Maternal height does not appear to play its customary ole as normal genetic determinant of stature prior to operation in the gro p of children at or beneath the 10th percentile for height, whereas after surgery accele ation in growth is correlated w th maternal height (169)

Patent ductus arteriosus with pulmonary hypertension. In the a topsy series reported by Abbott (1) of 1000 patients with congenital he rt disease total of 92 patients had a p tent ductu it rio sus, 20 of the latter had died in inf ncy Incr sing attention began to be paid to this ir umst nce at the end of the 1940s, when wide pen ductu was reported as the sole autopsy finding in an infant who had died at the age f 6 week (48) Part of th patients w th a patent ductus exhibit many symptoms, growth is retarded in most of them and occasionally congestiv heart failure develops as early as on the second day of life (73 81)

Because of pulmonary hypertension the continuous murmur is not audible and establishment of the diagnosis requires heart catheterization in most cases (30) Ziegler (175) was the first to demonstrate in 1952 the value of early operation Since that time numerous reports have been published from many countries on series of 4 208 patients with patent ductus operated upon under the age of 2 years, a successful operation resulting in disappearance of the symptoms and a definite acceleration of weight growth (6 19 39 60 97 110, 146 167) Grumbach and his co-workers (73) presented in 1968 five newborn who died at ages of 1 4 days with respiratory difficulty and congestive heart failure and whose sole autopsy finding was a wide ductus. Joly and co-workers (81) reported an excellent result of surgery on a 2-day-old newborn infant.

Operation as early as possible is recommended for all patients with patent ductus who exhibit symptoms, particularly if signs of pulmonary hypertension are present, since often the operation fully normalizes the hypertension.

It has been calculated that some 6 18 per cent f all cases of patent ductus arteriosus – in some series as many as 35 per cent (8) because of varying criteria are of this so-called atypical form (142 159) The surgical risk is considerable and even if defin it improvement is seen after operation in the clinical condition, objective findings and physical development, the situation will generally never be fully normal since the pulmonary vascular resistance does not revert to its normal level.

Coarctation of the aorta. Coarctation of the aorta is in principle f two types the infantile form which leads to severe congestive heart failure in infancy when surgical operation may be life saving, and the adult fo m which gives [illegible] relatively few symptoms (27) Growth is in general [illegible] considered to be normal in the latter [illegible] 102 116 127) However the patient [illegible] operated o by Crafoord was a 12-ye r [illegible] boy (44), and the series presented by [illegible] and Drash in 1962 (121) included among [illegible] 71 children with coar tation f the [illegible] preoperative mean height and weight [illegible] normal height being [illegible] weight and whose operation [illegible] fect both [illegible] his co-work reported in [illegible] hildren with coarct [illegible] operative [illegible] weight Following [illegible] of both the [illegible] growth The age at [illegible]

ny influence on the postoperative changes in height and weight provided surgery was undertaken before the age of puberty

Mortality is very high in conservatively treated ... the infantile form varying in different ... between 65 and 80 per cent (122 128). Surgical treatment is therefore considered to be indicated if definite improvement in the condition is not obtained with medical treatment. Mustard (13) was the first to undertake surgery for infantile coarctation in a patient only 11 days old with good results. Later there have been published series of 5–31 infants treated surgically for coarctation at various ages under 1 year (31 122, 1 3 1 8 134 160) with mortality in the range of 0 37 per cent. The most severely affected patients arrived for treatment when less than 1 month old because of severe congestive heart failure; in all later admitted cases one of the symptoms was retardation of growth, which was clearly accelerated after operation.

Tetralogy of Fallot. Growth disturbance is a widely recognized condition in all congenital heart diseases of the cyanotic group (37 49 61 91 106 121). Body weight of children with Fallot's tetralogy has been found to lag more than height (37). However Adams and his co-workers observed in 1945 (4) that physical development need not necessarily be retarded. Likewise Dry and his co-workers, in 1947 (51) stated that physical development may be quite good, and Parker in 1948 (13) was surprised to find how seldom the children's physical development was retarded in spite of the severe circulatory incapacity. These studies were made on series 4–66 patients.

Relatively few investigations are available on the influence of surgery on the growth of patients with the tetralogy of Fallot although in other respects their postoperative condition has been followed up for already some length of time (34 133 165). The first child in whom the Blalock Taussig anastomosis operation was performed (25) was a prematurely born child aged 1 year 3 months who weighed 4 kg at the time of operation and showed very good weight acceleration after the operation.

Bakhtina and her co-workers (15) are of the opinion that the weight of children with Fallot's tetralogy generally begins to lag at about the age of 6 months but the height rarely at under 3 years. Palliative surgery has been found to have a favourable effect on height and weight growth (.., 16 70 58 121 144) in series ranging from 1 to 786 patients. The smallest material is the presentation by Banik and co-workers (16) of a patient 18 7 years of age whose growth at the time of operation was at about the level of a 8.5-year-old and a year after the anastomosis operation showed catch-up to about 13.5 years. The beneficial effect of a palliative operation was thus clearly demonstrated even in a patient of this age

There also are reports of no effect on growth by palliative operations in series ranging from 47 to 141 patients (108 114 116 125). Baker and co-workers, writing in 1949 (14) expressed disappointment over the slight postoperative weight acceleration despite marked improvement in subjective health and physical capacity and assumed this circumstance to be due to the greater physical activity

A report in which the data are presented separately for the two sexes shows that boys with the tetralogy of Fallot are more greatly retarded in growth than girls (20). According to the same study there is improvement in girls' growth during the second decade regardless of whether or not surgery has been performed, and thus the difference between the sexes increases. This may be due to the earlier age of puberty of girls. By contrast Linde and co-workers (106) observed that retardation in height of girls with TF increases with age.

To summarize this review of the literature it is seen that growth may be retarded in all forms of congenital heart disease. Generally the weight lag is greater than the lag in height, and boys are more greatly retarded than girls. The growth disturbance is most clearly evident in the cyanotic group of congenital heart diseases. Surgical operation has been demonstrated to have a favourable effect on growth even if the results of the various studies have not been consistent. In studies in which the patients' height and weight growth has been observed during a number of years after surgery it has been found that acceleration in weight occurred within some months, or during the first postoperative year while catch-up in height sometimes required the first two postoperative years (50 58 95).

Object of the investigation

The object of the present work was to study the height and weight growth of children affected with certain types of congenital heart disease, and the effect of surgery on their growth.

The principal object was to obtain, in the light of the series of patients studied, answers to the following questions:

1) Do children with congenital heart disease *differ in height and weight growth from healthy* children of the same age?
2) Does heart surgery accelerate height and weight growth?
3) Are height and weight influenced to the same *extent?*
4) Are there differences between the sexes.
5) Does the age at operation have any influence on the postoperative height and weight growth?
6) How do the different types of congenital heart disease studied differ with respect to their effect on height and weight growth?
7) Are height and/or weight growths correlated with any of the following factors physical capacity predisposition to *infectious diseases*, congestive heart failure, electrocardiographic changes, heart size and certain specific factors connected with the type of congenital heart disease?

have any influence on the postoperative changes in height and weight provided surgery was undertaken before the age of puberty

Mortality is very high in conservatively treated cases of the infantile form varying in different statistics between 65 and 80 per cent (1 1 8) Surgical treatment is therefore considered to be indicated if definite improvement in the condition is not obtained with medical treatment Mu t rd (1.3) was the first to undertake surgery for infantile coarctation in a patient only 11 days old with good results. Later there have been published series of 5–31 infants tre ted surgically for coarctation at various ages under 1 ye r (31 1 ? 123 1 8 134 160) with mortality in the range of 0–37 per cent. The mo t severely affe ted patients arrived for treatment when less than 1 month old because of severe congestive heart failure in all later admitted cases one of the ymptoms was retardati n of growth, which was clearly accelerated after operation.

Tetralogy of Fallot. Gr wth di turbance is a widely recognized condition in all congenital heart diseases of the cyanotic group (37 49 61 91 106 121) Body weight of children with Fallot s tetralogy has been found to lag more than height (37) However Adams and his co-workers observed in 1945 (4) that physical development need not necessarily be retarded Likewise Dry and his co-workers, in 1947 (51) stated that physical de elopment may be quite good and Parker in 1948 (13) was surprised to find how seldom the children s physical development was retarded in spite of the severe circulatory incapacity These studies were made on series 4–66 patients.

Relatively few in estigations are a ailable on ie influence of surgery on the growth of patients with the tetralogy of Fallot although in other respects their postoperative condition has been followed up for already some length of time (34 133 165) The first child in whom the Blalock Taussig anastomous operation was performed (.5) was a prematurely born child aged 1 year 3 months who weighed 4 kg at the time of operation and showed very good weight acceleration after the operation.

Bakhtina and her co-workers (15) are of the opinion that the weight of children with Fallot s tetralogy generally begins to lag at about the age of 6 months but the height rarely at under 3 years. Palliative surgery has been found to have a fa ourable effect on height and weight growth (2, 16 20 58 1?1 144) in series ranging from 1 to 786 patients. The smallest material is the presentation by Banik and co-workers (16) of a patient 18 7 years of age whose growth at the time of operation was at about the level of a 8.5-year-old and a year after the anastomosis operation showed catch-up to about 13.5 years. The benefical effect of a palliative operation was thus clearly demonstrated even in a patient of this age.

There also are reports of no effect on growth by palliative operations in series ranging from 47 to 141 patients (108 114 116 1.5). Baker and co-workers, writing in 1949 (14) expresed disappointment over the slight postoperative weight acceleration despite marked improvement in subjecti e health and physical capacity and assumed this circumstance to be due to the greater physical activity

A report in which the data are presented separately for the two sexes shows that boys with the tetralogy of Fallot are more greatly retarded in growth than girls (20). According to the same study there is improvement in girls growth during the second decade regardless of whether or not surgery has been performed, and thus the difference between the sexes increases. This may be due to the earlier age of puberty of girls. By contrast Linde and co-workers (106) observed that retardation in height of girls with TF increases with age.

To summarize this review of the literature it is seen that growth may be retarded in all forms of congenital heart disease Generally the weight lag is greater than the lag in height, and boys are more greatly retarded than girls. The growth disturbance is most clearly evident in the cyanotic group of congenital heart diseases. Surgical operation has been demonstrated to have a favourable effect on growth, even if the results of the arious studies ha e not been consistent. In studies in which the patients height and weight growth has been observed during a number of years after surgery it has been found that acceleration in weight occurred within some months, or during the first postoperative year while catch-up in height sometimes requred the first two postoperative years (50 58 95)

the child's siblings, parents, parents siblings and and their children, and grandparents.

Table 2. *Congenital anomalies in close relatives, pregnancy and delivery complications and birth weight of the patients, in different diagnostic groups*

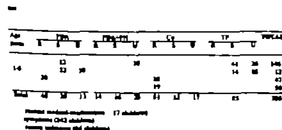
Diagnosis	Anomalies in close relatives	Of which cardiac defects	Complications during pregnancy and delivery	Mean birth weight kg [4]	Birth weight <2500 Number	Per cent
	Number of parents					
PDA	[illegible] ([illegible] M, 3 F)		2[1]		4/[illegible]	1
PDA+PH	([illegible] M, F)	3	3[2]	3.0	13/52	25.0
Co	([illegible] M, 3 F)		3[3]	3	1/[illegible]	1
TF	11 ([illegible] M, F)	10	3	3.3	[illegible]/[illegible]	9.8
Total	33 ([illegible])	20	[illegible] ([illegible])	3 kg	27/13[illegible][4]	

1) Rubella [illegible] [illegible]
2) Rubella [illegible] [illegible]
3) Suspected rubella [illegible] [illegible]
4) Birth weight was known [illegible] 138 cases

Table 3 *Extracardiac congenital anomalies in the different diagnostic groups*

Diagnosis	Skeleton	Sensory	Mental retardation	Others	Total number of children
PDA	1	4	2	3	10 (3 M, 7 F) (10 %)
PDA+PH	5	5	2	2	13 (3 M, 10 F) (23.6 %)
Co	3	1	1	2	7 (6 M, 1 F) (7.8 %)
TF	9		6	6	23 (1[illegible] M, 9 F) (23.0 %)
Total number of anomalies	18	1	11	13	54 anomalies in 53 children (14.9 per cent of the series)

Table 4 *Age at diagnosis of the congenital heart disease and reason for examination in the different diagnostic groups*



Height and weight measurements are compared with the standards btained by the Finnish Centre for Study in Child Growth and Development (12, 162). Using the respective standard growth curves of the above study each child's relative values of height and weight were calculated by assigning a value of 1000 to th mean height and weight in the curves (50th percentile) and a value of 100 to each 1 standard deviation. Thus, for example a measured value that is 1 SD below the mean (i.e at the 16th percentile) will have a value of 900 and a measured value 1 SD above the mean (at the 84th percentile) will be 1100

The distribution of measured heights and weights in relation to the above stated standard growth curves is presented in the form of graphs.

The height and weight measurements were made by an experienced staff always using the same equipment

Physical capacity was assessed from the case history obtained, also giving consideration to the child s physical activity while in the hospital Parents information on the child's progress after operation was also considered in making the evalution at follow-up examination. Physical capac ity equivalent to age was indicated by 0 A child that became breathless clearly more readily than others of his age was given the score 1 Score 2 designated a reduced physical capacity that clearly placed limitations on a life compatible with age, and 3 indicated physical capacity that was so greatly reduced that the patient was unable to walk more than 100 metres. Physical capacity is thus used as a means of assessing the patient s ability to cope with his environment.

Predisposition to infectious diseases was estimated by comparing the number of instances of infectious illnesses in the child s past history with those of his siblings and playmates and of the series observed by the Finnish child growth study group (13)

At *auscultation* the intensity of heart murmurs was graded from I to VI (104)

Congestive heart failure was diagnosed on the base of the usual criteria.

Blood pressure was measured at each examination. The upper limit of normal systolic pressure was considered to be 120 mm Hg and values below this limit were indicated by 0 Systolic pressure of 121 149 mm Hg was recorded as 1 150-199 mm Hg as 2, and 200 mm Hg or over as 3

Of the *laboratory test results* haemoglobin (Hb) values were studied in every case and those of haematocrit (Hcr) since 1962.

Interpretation of electrocardiograms. The complete electrocardiogram was recorded in all cases, i.e. standard leads, unipolar limb leads and chest leads V_1 V_6, if necessary also V_4R. Exceptions were two infants with TF who because of their grave condition were submitted to surgery immediately [illegible] limb lead electrocar d[illegible] th e t o cases be-

Material and methods

The series studied consists of 355 patients who had undergone surgery in the Children's Hospital, University of Helsinki. The first operation included in the study was performed in 1953 and the last ones in 1967. Details of the series appear in Table 1.

Table 1. *The material according to diagnosis, special examinations performed and sex.*

Diagnosis	Catheterization and/or angiocardiography	Boys	Girl	Total
PDA		27	73	100
PDA+PH	55	13	42	55
Co	56	78	22	100
TF	88	6	38	100
Total	199	180	175	355

Classification of diagnoses and selection of cases for study (Table 1)

Patent ductus arteriosus (PDA). This group is comprised of 100 consecutive patients who were operated on for this defect in the period from January 1961 to July 1963. The continuous murmur was audible in all the cases and no signs of pulmonary hypertension were found. Special examinations were not made; at operation the diagnosis was found to be correct.

Patent ductus arteriosus with pulmonary hypertension (PDA + PH). In this group are the 55 patients with the above diagnosis who had undergone operation up to the end of 1967 and on whom the necessary data were available. The first operation had been made in April 1958 and the last in April 1967. For establishment of the diagnosis heart catheterization was performed before operation in all cases. In all patients the systolic pulmonary arterial pressure was over 50 mm Hg and right ventricular hypertrophy was evident in the electrocardiogram.

Coarctation of the aorta (Co). This group consists of the first 100 operated patients with this diagnosis on whom the necessary data were available. The first operation was performed in 1955 and the last ones in 1966. All the patients had the typical coarctation of the aorta, in addition to which 10 patients had a narrowly open ductus which was closed during the same operation. In 5 patients with coarctation there also was found an aortic valvular abnormality of mild degree which was not considered to have significance clinically. The more complicated cases as well as patients with Turner's syndrome were excluded from the group. Heart catheterization and/or angiocardiography and/or aortography were performed preoperatively on 56 patients for verification of the diagnosis.

Tetralogy of Fallot (TF). This group includes the first 100 patients with this diagnosis on whom palliative surgery was performed and the necessary data were available. The first operations were made in 1953 and the last ones in 1967. The diagnosis was established before operation by special examinations in 88 cases, and in 12 cases it was based on clinical, electrocardiographic and roentgenologic examinations.

Methods of study

The patients have been under the observation of the cardiac department of the Children's Hospital. Included in the present report is the condition of the child at examinations made immediately before operation and about one year after operation. The postoperative examination of 70 per cent of the patients was made 1 year ± 7 days after operation; the latest exceptional date of postoperative examination was 2 years in the case of two girls with TF and the earliest was 0.42 year for a girl with PDA+PH. Thus the mean observation time of the total series was 1 year 15 days ± 1.04 year.

Information on *heredity, pregnancy, delivery and birth weight* as well as on *extracardiac congenital anomalies* and the *age at diagnosis of the heart disease* was collected in as great detail as possible (Tables 2, 3 and 4). The close relations include

ing re-thoracotomy (2 cases) empyema (1) obstruction of a Blalock Taussig anastomosis leading to a new operation, tracheal stricture (in a child intubated for 6 days) and paresis of the recurrent nerve (1).

Table 7 *Age at operation in the different diagnostic groups*

Diagnosis	Age (years)		Number of patients			
	Range	Mean	7 years	10 years	11 years	Total
PDA	0 15 0	(6 7 M, 7.3 F)	30	1	21	100
PDA+PH	3 15 0	7 0 (8 6 M, 6.3 F	27	13	13	53
C	0 3-15 0	8 (8.8 M, F)	21	43	36	100
TF	2 10 0	3 (7 2 M, 7 6	49	29	22	100
Total	2 15 0		135	128	92	353

[illegible]

Table 8 *Surgical techniques in the different diagnostic groups*

Diagnosis	N of patients	Technique
PDA	99	Ligatura
	1	Discisio
PDA PH	14	Ligatura
	37	Discisio
	4	Application of bulldog forceps 1)
Co	98	Resectio et reanastomosis
	2	a m Clagett
TF	94	Anastomosis a m Blalock Taussig
	1	art. mammaria int t art pulm dx
	3	Valvulotomia m Brock
Total	355	

1) Technique devised by Salama (161) for especially difficult cases of PDA + PH in 1960–1961 before use of extracorporeal circulation in this hospital

Table 9 *Postoperative complications in the different diagnostic groups*

Diagnosis	Re-operations	Infections	Minor [illegible]	[illegible]	Others	Total	
						Number	Per cent
PDA							
PDA PH		2				[illegible]	[illegible]

Table 10 presents the surgical mortality in all cases of the studied diagnostic categories treated surgically in this hospital during the period of the study

Table 10. *Surgical mortality in the period studied, based on total number of operations including patients excluded from the study because of incomplet data*

Diagnosis	Number of boys	Mortality Number	%	Number of girls	Mortality Number	%	Total number of operations	Total mortality Number	%
PDA	27		0	73			100		
PDA+PH	1	2				8.5	64		
C	88		10 2	23[1]	2	3	1)	10[2]	
TF	60			39		2.6	100	1	
Total	281			182	[2]	3	363	[2]	3

[illegible]
2) [illegible]

Statistical analysis of the results was carried o t at the Computing Centre of the University of Helsinki. Student's t-test was used in tudying the significance of differences of the means, additionally the results were compared by means of correlation coefficients. The difference is considered to be highly significant when $p < 0.001$ significant when $p < 0.01$ and almost significant when $p < 0.05$

The criteria for hypertrophy applied in the present work are as follows (37 88 96 175).

Criteria for right ventricular hypertrophy (RVH)

1) Voltage of R in V_1 greater than maximum normal for age (175)
2) Voltage of R in V_6 greater than maximum normal for age
3) R/S ratio in V_1 greater than maximum normal for age.
4) Positive T in V_1 after third day of life
5) A q wave in V_1 after third day of life
6) Ventricular activation time greater than upper limit of normal for age in right precordial leads.

Criteria for left ventricular hypertrophy (LVH)

1) Voltage of R in V_6 greater than maximum normal for age
2) Voltage of S in V_1 greater than maximum normal for age
3) R/S ratio in V_1 less than minimum normal for age.
4) Secondary T inversion in V_5 and/ or V_6
5) Deep Q over the left precordium.
6) Ventricular activation time greater than upper limit of normal for age in left precordial leads.

Criteria for combined ventricular hypertrophy (CVH)

1) Direct signs of right plus left ventricular hypertrophy (as above)
2) Direct signs of right ventricular hypertrophy with the following signs in left chest leads
a) q wave (2 mm or more)
b) sizable R (voltage not necessarily abnormal) with tall, positive T
c) T inversion after a positive T in right chest leads ventricular activation time in V_6 greater than in V_1
3) Direct signs of left ventricular hypertrophy with
a) sizable R or R in right chest leads (voltage not necessarily abnormal) or R/S ratio greater than 1.0
b) ventricular activation time in V_1 greater than in V_6

The assessment of electrocardiograms is always subjective All the electrocardiograms were reviewed and assessed by the writer The degree of hypertrophy is indicated with 1 2 3 according to the number and intensity of lectrocardiographic changes, degree 3 being the mo t severe

Evaluation of heart size from roentgenograms was one of the procedures at each examination. In the earlier years this was done in anterior posterior projection by measuring the cardiothoracic ratio, i.e. the ratio of the maximum width of the heart to the width of th bony thorax at the level of the diaph agm The values garded in this study as normal and the grades of enlargement (14 21 36 52 77 116 167 169) are stated in Table 5 Since 1959 the absolute heart volume has been determined routinely by the Rohrer Kahlstorf method as modified by Jonsell (86) The method is a simple one and is considered to be adequately reliable for observation of the heart size of one and the same patient in the same hospital (93)

Table 5 *Upper limit of normal ardio-thoracic ratio (0) and grades f ardiac enlargement at d fferent ages, as used in this study*

Age years	Heart size per cent			
	0	1	2	3
<1	55	55-60	60-65	>65
1 5	50	50-55	55-60	>60
_6	<45	45-50	50-55	55

As is well known, heart size correlates very closely with the individual s body surface area and therefore the relative heart volume is generally expressed in millilitres per square metre of body surface area (ml/m^2 BSA)

In childhood the relative volume of the heart is age-dependent (38 90 93 105) Table 6 shows the values regarded in the present work as the upper limits of normal and the grades of enlargement at different ages.

T ble 6 *Upper limit of normal relative heart volume (0) and grades of cardiac enlargement at different ages, as sed in this study*

Age years	Heart size ml/m^2 BSA			
	0	1	2	3
< 1	270	270-300	300-400	400
1 2	330	330-400	400-500	500
3-6	350	350-450	450-600	600
7 11	400	400-500	500-650	>650
≧1	450	450-550	550-700	700

Surgical techniques and complications The children s ages at the time of operation (Table 7), the surgical procedures used (Table 8) and the complications associated with the operation (Table 9) appear from the tables. Of the further complications (Table 9) may be mentioned lesion of the spinal medulla on the base of anoxia and consequent mild paresis of the lower extremities in a patient with coarctation. Another patient with Co developed recoarctation within the first year after operation. Additional complications were among other conditions, haemorrhage requir-

value of one boy in the oldest age group (operation at 11 years or over) declined, however post operatively by slightly less than 1 SD

Physical capacity was reduced in 18 boys with PDA before operation and the mean preoperative capacity value of the group of 27 boys was –0 67 Postoperatively the physical capacity of all the patients was normal.

Predisposition to infectious diseases was present before operation in 10 boys and after operation in one boy

No signs of *congestive heart failure* were seen in any of the cases.

Pulse pressure preoperatively was mean 60 mm Hg and postoperatively 38 mm Hg.

Electrocardiography showed no signs of right ventricular hypertrophy in any of the boys. There were signs of left ventricular hypertrophy in 18 cases before operation and in 3 of these patients after operation. The mean value of hypertrophy was 0.93 preoperatively and 0 11 postoperatively

Heart size in relation to age was larger than normal in 15 boys before operation and still after operation in 5 of these. The preoperative mean was 0.93 and the postoperative mean 0 19 In 6 boys the size was reduced after operation although it had been within normal limits already before operation.

Effect of age at operation (Table 12) If the boys are divided according to age at operation into three groups as follows. 11 boys under 7 years, 7 boys 7 10 years and 9 boys 11 years or over the groups will be so small that comparisons between them will not be useful. It may be mentioned however that the greatest benefit from the operation was seen in both height and weight growth in the group submitted to surgery at the earliest age. Also the decrease in heart size was most notable in this group

Effect of additional factors. No difference in mean height or weight from the rest of the group was found in the boys who had been born prematurely (1 boy) in those among whose close relations there were known to be congenital anomalies (3 boys) or in those in whom an extra-cardiac congenital anomaly had been diagnosed (3 boys, Tables 2 and 3)

Girls (73 cases, Table 13)

Height and weight growth. The preoperative mean height value (967 40) was significantly and the mean weight value (947.23) highly significantly below normal. About a year after operation (mean 1 year 5 days = 1 01 year) the mean height (998 71) and mean weight (986 15) did not differ from the normal.

The percentile distributions (Figs. 3 and 4) show that before operation a greater proportion of the girls than normally were in the lowest channels both in heihgt (28 7 per cent) and in weight (32 9 per cent) There was definite shift upwards into higher channels after operation in some cases, the postoperative distribution being

Table 12. *Effect of age at operation. PDA group, boys (27 cases)*

Age at operation ⟶	1 < 7 years (11 boys) Mean	SD	2 7 10 years (7) Mean	SD	3 ≧ 11 years (9) Mean	SD	p between groups 1 2	1 3	2–3
Preoperative height	932 82	112 31	859.86	131 00	975 00	92 56			<0 05
weight	922.55	119 89	856 43	94 89	1001 78	95.57			<0 01
physical capacity	–0 82	0 40	–0 57	0 53	–0 56	0 53			
heart volume ml/m² BSA	442 73	110 91	417 14	88 64	431 11	60 71			<0 01
Postoperative height	972 82	121 29	877 57	118 17	968 67	89 53	0 05		
weight	993 82	142 46	875 57	89 75	1016 78	124 04		0 01	
heart volume ml/m² BSA	334 09	35 97	347 14	49 90	390 00	38 41			
not significant									

Table 13 *Results of girls in the PDA group (73 cases)*

	Height Mean	SD	Weight Mean	SD	Physical capacity Mean	SD	Predisp. to infections Mean	SD	Pulse pressure Mean	SD	VH Mean	SD	Heart size Mean	SD	Heart ml/m² BSA Mean	SD
Preop	96 40	108	947 23	42	–0 45	0.60	[illegible]	0.30	60	83	22	30	73	2	13.08	94 85
Postop	998	27	986 15	30 52	00	00	00	0.00	40 83		25	43		0.35	339.84	85 78
p	05		<0 05		00		<0 001		001		<0 001		<0 001		001	

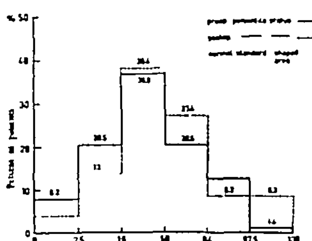


Fig. 3. Girls with patent ductus arteriosus. C mparison of height percentile status distribution before and after surgery with normal standard for Finnish children (12, 162)

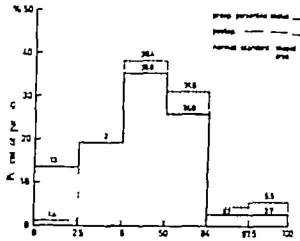


Fig. 4. Girls with patent ductus arteriosus. Comparison of weight percentile statu distrib tion befor and after surgery with normal standard for Finnish children (12, 162)

quite close to normal. Preoperative individual deviations in height and weight were up to −3 SD. The greatest individual postoperative rise was over +2 SD in both height and weight. The preoperative mean deviation was about −0.3 SD in height and about −0.5 SD in weight and the mean post-operative change was about +0.3 SD and about +0.4 SD respectively. However the height and weight values of two girls in the oldest age group declined postoperatively by slightly less than 1 SD.

Physical capacity before operation was reduced in 37 girls, the mean value of the 73 girls being −0.45. After operation the physical capacity of all the girls was normal.

Predisposition to infectious diseases was present in 30 girls before operation and in none after operation.

Signs of *congestive heart failure* were not seen in any of the girls in the PDA group.

Pulse pressure was preoperatively mean 60 mm Hg and postoperatively mean 41 mm Hg.

Electrocardiography revealed preoperatively right ventricular hypertrophy in two girls and postoperatively in one of them. Neither of them showed signs of pulmonary hypertension. Both girls had marked enlargement of the heart prior to operation.

Left ventricular hypertrophy was seen preoperatively in 54 girls. After the operation it was reduced in all of them but was still present in 16. Preoperatively the mean LVH was 1.22 and postoperatively 0.5.

Heart size was increased above normal in 31 girls before operation, the group mean being 0.73. Postoperatively the heart had decreased in size in all of these patients but in 8 it still remained above normal in relation to age; the mean value was 0.14. The hearts of 30 other girls, which preoperatively had already been within normal limits, decreased postoperatively.

Effect of age at operation (Table 14). When the girls with PDA are distributed into three

Table 14 *Effect of age at operation. PDA group, girls (73 cases)*

Age at operation ——→	1 < 7 years (27 girls)		2 7–10 years (34)		3 ≧ 11 years (12)		p between groups		
	Mean	SD	Mean	SD	Mean	SD	1–2	1–3	2–3
Preoperative height	977.63	137.71	968.03	93.79	942.58	74.16			
weight	941.48	153.78	954.65	83.05	939.17	53.76			
physical capacity	−0.52	0.51	−0.38	0.49	−0.50	0.52			
heart volume ml/m² BSA	409.63	104.86	411.32	85.33	425.83	99.22			
Postoperative height	1027.56	135.49	996.50	90.93	940.08	92.20		< 0.05	< 0.05
weight	1025.00	184.16	975.21	78.75	929.75	72.12		0.05	< 0.05
heart volume ml/m² BSA	307.78	43.35	348.24	48.77	383.33	63.15	0.001	0.001	< 0.05

not significant

groups according to the age at operation, i.e. 27 girls under 7 years, 34 girls 7 10 years, and 12 girls 11 years or over a comparison shows that the mean height and weight values of the oldest girls were the lowest, even if the differences between the groups were not statistically significant. After operation their mean height and weight values went slightly down and were almost significantly lower than in the other groups. The greatest postoperative catch-up in height and weight occurred in the group operated on at the lowest age, in which the postoperative mean values were slightly above the normal. Reduction in heart size after operation was most clear in the youngest group.

Effect of additional factors. A comparison between the girls with PDA who had some additional factor prematurity (3 girls) congenital anomalies in close relations (5), or own extracardiac congenital anomaly (7 Tables 2 and 3) with the rest of the group revealed no difference either in height or in weight.

Comparison between boys and girls (Table 15)

Comparison of the boys and girls in the PDA group showed a slightly greater retardation in preoperative mean height and weight in boys than in girls, although the differences had no statistical significance. Postoperatively the mean height value of boys was almost significantly below that of girls. The postoperative mean weight value was also slightly lower in boys than in girls but the difference was not of statistical significance.

Prior to operation the physical capacity of the boys was almost significantly poorer than that of the girls.

Predisposition to infectious diseases persisted in one boy after operation but in none of the girls.

The results of other examinations revealed no differences between boys and girls either pre- or postoperatively

Correlations between the various factors (Table 16)

These were studied by means of correlation coefficients. Preoperatively there was an almost significant correlation between left ventricular hypertrophy and height lag, and a significant correlation between left ventricular hypertrophy and weight lag. Likewise weight lag was almost significantly correlated both with right ventricular hypertrophy and with the grade of intensity of the continuous murmur Postoperatively left ventricular hypertrophy was significantly correlated with both height and weight lag. The other factors studied (physical capacity predisposition to infectious diseases, pulse pressure diameter of ductus measured at operation) were not found to have a correlation with either height or weight growth.

Comparison between the other factors showed correlations between intensity of the continuous murmur cardiomegaly left ventricular hypertrophy and diameter of ductus. The physical capacity of children with predisposition to infectious diseases was poorer than that of non-predisposed children.

Summary of results in the uncomplicated PDA group

This group wa composed of 100 consecutive operations on children with patent ductus arteriosus. The sex distrib tion hanced t be 73 girls and 27 boys, the sex ratio thus being 2 7 1

Congenital anomalies had been diagnosed in close relatio s of 11 1 per cent of the boy and 6 9 per cent of the girls, i.e in 8 per cent f the group (Table 2)

Two m thers, e. 2 per cent, had had rubella infection in early pregnancy The mean birth weight of both boys and girls was normal and prematurity in the PDA group (Table 2) was not more commo than in the general population of Finland

Table 15 *Comparison between boys (27 cases) and girls (73 cases) in the PDA group*

	Height Preop	Height Postop	Weight Preop	Weight Postop	Physical capacity Preop	Physical capacity Postop	Predisp. to infections Preop	Predisp. to infections Postop	Murmur Preop	Murmur Postop	Pulse pressure Preop	Pulse pressure Postop	VH Preop	VH Postop	Heart size Preop	Heart size Postop	Heart volume/BSA Preop	Heart volume/BSA Postop	Diameter of ductus
Boys	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Girls	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
p		[illegible]			[illegible]			[illegible]	[illegible]	[illegible]								[illegible]	

not significant

Table 16 *Correlation coefficients in the PDA group (100 patients)*

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Preoperative height	1	999																			
weight	2	796	999																		
physical capacity	3	102	029	999																	
predisposition to infections	4	007	105	310	999																
continuous murmur	5	-080	-223	094	177	999															
pulse pressure	6	-104	145	140	080	170	999														
RVH	7	144	229	086	034	199	-072	999													
LVH	8	-251	.71	003	055	3.4	152	255	999												
heart size	9	071	117	176	324	371	234	216	413	999											
volume ml/m² BSA	10	-116	-104	160	232	321	234	192	495	885	999										
Diameter of ductus	11	-100	129	014	007	205	180	016	274	300	342	999									
Postoperative height	12	877	724	121	125	070	051	145	154	048	048	018	999								
weight	13	722	883	-058	029	-128	-035	-165	-184	031	-022	001	753	999							
predisposition to infections	14	039	125	-099	1.3	176	202	017	130	-084	096	070	049	153	999						
systolic murmur	15	182	-2.3	033	096	238	050	.29	264	186	2.3	158	088	162	-059	999					
pulse pressure	16	085	087	014	159	101	263	042	058	166	002	074	071	026	050	051	999				
RVH	17	150	147	103	082	220	058	815	212	131	111	010	146	-104	-010	167	-001	999			
LVH	18	342	285	112	030	160	-065	219	474	069	151	050	287	263	052	168	040	195	999		
heart size	19	138	127	132	229	091	065	046	314	429	528	159	148	149	-042	195	007	-042	127	999	
volume ml/m² BSA	20	094	200	044	060	016	-091	031	249	295	5.4	012	017	078	0 8	077	101	028	093	679	999

p	<0.05	197
	<0.01	257
	<0.001	324

Significant correlations are underlined

Extracardiac congenital anomalies had been diagnosed in 11 1 per cent of boys and 9.6 per cent of girls, the group incidence being 10 per cent (Table 3)

The age at diagnosis of the PDA ranged from newborn to 13 years, the mean age being 3 4 years for boys and 4.2 years for girls. In about half of the cases the diagnosis had been made at a routine medical examination and in over one-third at an examination because of symptoms; in the remaining cases no information was available on this point. In exactly one-fifth of the cases the defect had been discovered in the child s first routine medical examination by the school physician (Table 4).

The age at operation varied from 1.8 to 15.8 years, mean 8 4 years (Table 7)

The incidence of recanalization was 1 per cent (Table 9) and the surgical mortality during the period studied was 0 (Table 10)

Prior to operation the mean height and mean eight of both boys and girls were below the normal for Finnish children. One year after surgery the mean height of the boys continued to lag almost significantly but the mean weight was within normal limits. The mean postoperative height and weight of girls were in the normal range. Boys' values were slightly lower than those of girls, however the only statistically significant difference between the sexes was found in the postoperative mean height.

The greatest acceleration in mean height and weight after operation was seen, in the case of both boys and girls, in the group submitted to operation for PDA at the earliest age (under 7 years) Reduction in heart size also was most clearly evident in this group

The physical capacity of 50 children was reduced preoperatively but postoperatively was normal in all cases. A number of children who already preoperatively were considered to be normal improved still further after surgery

Following operation a predisposition to infectious diseases disappeared, pulse pressure decreased left ventricular hypertrophy diminished and heart size was reduced

Extracardiac congenital anomalies in the child and congenital anomalies in close relation were not found to have any significance f the child's height and weight growth

It was bserved in general that the louder the continuou m rmur was, the larger was the heart, the more marked the left ventricular hypertrophy and the larger the ductus Children w th cardiomegaly were more predisposed t infections than those with normal sized heart Physical capacity of infection-predisposed children was poorer than that of the others The degree of left ventricular hypertrophy correlated almost significantly adversely with height and weight. The other factors studied were not found to correlate with the physical growth of the children with PDA either before or after surgery

Discussion

The patent ductus arteriosus group had a predominance of girls (2 7 1) as is generally known to be the case (11 19 21 43 53 64 66 71 77 84 88 96 109 126 154 170)

In about half of the cases the congenital heart disease had been detected at a routine medical examination. This conforms well with other studies in which 11–65 per cent (11 21 41 98) or most of the cases (154) were found at routine medical examinations.

Complications during the pregnancy concerned and premature births were not more common in the present PDA group than in the general Finnish population (139 140) Some studies in the lit rature report considerably above normal incidences of prematurity in the range 9 0 13 4 per cent (11 95 98 116 170) and rubella, other virus diseases, haemorrhages and other pregnancy complications in 20 per cent of cases (11)

Extracardiac congenital anomalies had been diagnosed in 10 per cent of the children in this PDA group This is slightly less than in other similar clinical series, with incidences f 12 20 per cent (9 11 26 78 98 170) the rat being understandably still higher in utopsy series (24 100 101 130)

In the series published by Krovetz (95) there were more extracardiac congenital anomalies among the children who did not show acceleration of height and weight growth after surgery than in the other children Umansky and Hauck (168) observed likewise that patients with no xtracardiac congenital anomalies constitut large group in which stunting is relatively uncommon. In the present study no correlation was found between extracardiac congenital anomalies and height and weight growth either before or fter surgery for PDA.

The preoperative mean height and weight were below the normal standards for Finnish children Following surgery there was definit acceleration, nevertheless the mean height f boys remained almost significantly under the normal. Comparison of the percentile distributions in this series with the normal percentiles of Finnish children indicated that an unexpectedly large proportion of the small series f boys remained even after operation in the two lowest percentile channels f both height and weight, whereas the postoperative

Table 16 *Correlation coefficients in the PDA group (100 patients)*

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Preoperative height	1	999																			
weight	2	796	999																		
physical capacity	3	102	029	999																	
predisposition to infections	4	007	105	-310	999																
ontinuous murmur	5	080	223	094	177	999															
pulse pressure	6	104	145	140	080	170	999														
RVH	7	-144	229	086	034	192	072	999													
LVH	8	-251	271	003	055	3.4	152	255	999												
heart size	9	071	117	176	324	371	234	.16	413	999											
volume ml/m^2 BSA	10	-116	-104	160	232	321	234	192	495	885	999										
Diameter of ductus	11	-100	129	-014	007	.05	180	016	274	300	347	999									
Postoperative height	12	877	724	121	125	020	051	145	154	048	048	018	999								
weight	13	722	883	-038	029	-128	-035	-165	184	031	-022	001	753	999							
predisposition to infections	14	039	125	-099	123	176	202	-017	130	-084	096	070	049	153	999						
systolic murmur	15	-182	-2..3	033	096	238	050	.29	264	186	223	158	088	162	-059	999					
pulse pressure	16	085	087	014	159	101	.63	042	058	166	002	074	071	026	050	051	999				
RVH	17	150	-147	103	082	.20	-058	815	212	131	111	010	-146	-104	-010	167	-001	999			
LVH	18	342	285	112	030	160	-065	219	474	069	151	050	-287	.63	052	168	040	195	999		
heart size	19	138	127	132	229	091	065	046	314	429	528	159	148	149	-042	195	007	-042	127	999	
volume ml/m^2 BSA	20	094	200	044	060	016	-091	-031	249	295	524	012	017	078	028	077	101	028	093	629	999

P		
	<0.05	197
	<0.01	257
	<0.001	324

Significant correlations are underlined

Extracardiac congenital anomalies had been diagnosed in 11.1 per cent of boys and 9.6 per cent of girls, the group incidence being 10 per cent (Table 3)

The age at diagnosis of the PDA ranged from newborn to 13 years, the mean age being 3.4 years for boys and 4.2 years for girls. In about half of the cases the diagnosis had been made at a routine medical examination and in over one-third at an examination because of symptoms, in the remaining cases no information was available on this point. In exactly one-fifth of the cases the defect had been discovered in the child's first routine medical examination by the school physician (Table 4)

The age at operation varied from 1.8 to 15.8 years, mean 8.4 years (Table 7)

The incidence of recanalization was 1 per cent (Table 9), and the surgical mortality during the period studied was 0 (Table 10)

Prior to operation the mean height and mean weight of both boys and girls were below the normal for Finnish children. One year after surgery the mean height of the boys continued to lag almost significantly but the mean weight was within normal limits. The mean postoperative height and weight of girls were in the normal range. Boys' values were slightly lower than those of girls, however the only statistically significant difference between the sexes was found in the postoperative mean height.

The greatest acceleration in mean height and weight after operation was seen, in the case of both boys and girls, in the group submitted to operation for PDA at the earliest age (under 7 years). Reduction in heart size also was most clearly evident in this group

The physical capacity of 50 children was reduced preoperatively but postoperatively was normal in all cases. A number of children who already preoperatively were considered to be normal improved still further after surgery

Following operation predisposition to infectious diseases disappeared pulse pressure decreased, left ventricular hypertrophy diminished and heart size was reduced

Extracardiac congenital anomalies in the child and congenital anomalies in close relation were not found to have any significance for the child height and weight growth

It was observed in general that the louder the continuous murmur was, the larger was the heart, the more marked the left ventricular hypertrophy and the larger the ductus. Children with cardiomegaly were more predisposed to infections than those with normal sized heart. Physical capacity of infection-predisposed children was poorer than that of the others. The degree of left ventricular hypertrophy correlated almost significantly adversely with height and weight. The other factors studied were not found to correlate with the physical growth of the children with PDA either before or after surgery

Discussion

The patent ductus arteriosus group had a predominance of girls (2.7:1) as is generally known to be the case (11 19 21 43 53 64 66 71 77 84 88 96 109 126 154 170)

In about half of the cases the congenital heart disease had been detected at a routine medical examination. This conforms well with other studies in which 11–65 per cent (11 21 41 98) or most of the cases (154) were found at routine medical examinations.

Complications during the pregnancy concerned and premature births were not more common in the present PDA group than in the general Finnish population (139 140). Some studies in the literature report considerably above normal incidences of prematurity in the range 9.0 – 13.4 per cent (11 95 98 116 170) and rubella, other virus diseases, haemorrhages and other pregnancy complications in 20 per cent of cases (11)

Extracardiac congenital anomalies had been diagnosed in 10 per cent of the children in this PDA group. This is slightly less than in other similar clinical series, with incidences of 12–20 per cent (9 11 26 78 98 170) the rate being understandably still higher in autopsy series (24 100 101 130)

In the series published by Krovetz (95) there were more extracardiac congenital anomalies among the children who did not show acceleration of height and weight growth after surgery than in the other children. Umansky and Hauck (168) observed likewise that patients with no extracardiac congenital anomalies constitute a large group in which stunting is relatively uncommon. In the present study no correlation was found between extracardiac congenital anomalies and height and weight growth either before or after surgery for PDA.

The preoperative mean height and weight were below the normal standards for Finnish children. Following surgery there was definite acceleration, nevertheless the mean height of boys remained almost significantly under the normal. Comparison of the percentile distributions in this series with the normal percentiles of Finnish children showed that an unexpectedly large proportion of the small series of boys remained even after operation in the two lowest percentile channels of height and weight, whereas the postoperative

percentiles of girls corresponded to the normal ones in height and weight These observations are in agreement with those cited in the review of the literature

In the present study the greatest po toperative catch-up in both height and weight occurred in the children who had undergone operation at an early age under 7 years. This conforms well with some of the earlier studies in which the best improvement wa seen in children operated on when under 3 years (56 107 121) under 5 years (50) or generally at an early age (5)

Growth retardation was more marked in boys than in girls, as has been observed also in earlier studies of PDA patients (95) Studies in the literature report a greater lag in weight than in height (10 71 137 146) In thi tudy girl with PDA had lower weight values than height values before and after surgery while boys values were lower for height than for weight

It has been a sumed (57) and also confirmed (166) that the diameter of the ductus correlated with growth retardation, but it also has been found that the diameter of the ductus, measured at operation has no correlation with physical development (56) The latter was the observation also in the present study

It has also been suggested that retardation of growth would be a consequence of recurring respiratory infections in PDA patients (4 10 56) Maxwell and his co-workers (116) found no correlation between predisposition to infectious diseases and physical development nor wa such a correlation obtained in the present study

Improvement in the physical capacity took place even in children preoperatively considered to be normal in this respect and acceleration in weight growth occurred also in patients of normal weight, both of which are previous observations (11 56 63 91 107 153 155) Likewise a decrease has been seen even in hearts that were within normal limits before operation (11 6) as was observed also in the present work

An inverse correlation has been found between heart size and preoperative weight but not height (168) In this study no correlation wa seen between the heart size and the height and weight growth. On the other hand there wa observed an inverse correlation between left ventricular hypertrophy and height and weight both pre- and postoperati ely

Patent ductus arteriosus with pulmonary hypertension (PDA+ PH)

Boys (13 cases, Table 17)

Height and weight growth. The preoperative mean height value (901 23) and weight value (873.54) were statistically significantly below normal, which is denoted by the value 1000 About a year after operation (average 353 days = 0.98 year) the mean height (922.31) as well as the mean weight (897 69) were still almost signif icantly below normal.

In the percentile distribution of heights and weights (Figs. 5 and 6) over half of the boys with PDA+PH were preoperatively under the 16th percentile both in height (53 9 per cent) and in weight (61 6 per cent) Although after operation there were slight rises into higher channels, a considerable proportion of the boys remained under the 16th percentile in height (46.2 per cent) and especially in weight (61.6 per cent). The greatest individual deviation preoperatively was over −3 SD in both height and weight postoperatively the greatest individual increases from the preoperative values were slightly over +0.5 SD in height and over + 1 SD in weight. The mean preoperative height value was −1 SD and weight value −1.3 SD and the mean postoperative increase from these values+0.2 SD in height and slightly less than +0.3 SD in weight

Physical capacity was, with one exception, decreased in all cases, the mean capacity of the group being 1 Operation brought improvement in 9 boys, although only 5 of these attained the normal level the group mean being −0.23.

Predisposition to infectious diseases was present preoperatively in 6 boys (group mean 0 46) the pathological tendency to infections disappeared postoperatively

Signs of *congestive heart failure* were present before surgery in 2 boys in the group operated on at the earliest age but were no longer present after operation

The mean *pulse pressure* was 61 mm Hg preoperatively and 40 mm Hg postoperatively

The *systolic pulmonary arterial pressure* was mean 86.5 mm Hg before surgery and 55.3 mm Hg a year later The systolic pressure declined in

Table 17 *Results f boys in the PDA PH group (13 cases)*

	Height		Weight		Physical capacity		Predisposition to infections		Pulse pressure		Syst. pressure		[illegible]		[illegible]		[illegible]		[illegible]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Preop	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Postop		[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
						[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]

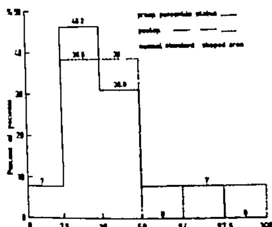


Fig. 5. Boys with patent ductus arteriosus with pulmonary hypertension. Comparison of height percentile status distribution before and after surgery with the normal standard for Finnish children (12, 162)

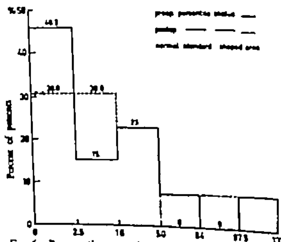


Fig. 6. Boys with patent ductus arteriosus with pulmonary hypertension. Comparison of weight percentile status distribution before and after surgery with the normal standard for Finnish children (12, 162)

all the cases, though in 3 the reduction was only 10 mm Hg or less. The greatest fall, from 115 to 35 mm Hg, occurred in a boy who underwent operation at 6 months. Postoperative measurement of pulmonary pressure was not made in one case, but clinically the boy exhibited distinct signs of a marked fall in pressure. In the postoperatively catheterized cases the preoperative pulmonary arterial pressure had been mean 85.8 mm Hg.

Electrocardiography. Right ventricular hypertrophy was seen preoperatively in all of the 13 boys with PDA+PH. The group mean of 1.62 decreased to 0.85 postoperatively when signs of hypertrophy were still present in 6 cases.

ECG signs of left ventricular hypertrophy were seen in 7 boys preoperatively and still in 2 of these postoperatively the group mean being 1.62 and 0.46, respectively.

Heart size was above normal in all the patients before operation and in 11 patients after operation, the respective means being 2.0 and 0.92. The relative heart volume was also greater than normal before operation (567.7 ml/m^2 BSA) and decreased postoperatively (441.5).

Effect of age at operation. In view of its small size, distribution of the group by age at operation does not give valid data on this point. It could be observed, however that 2 out of 4 boys submitted to surgery at under 7 years moved into a higher percentile of height and weight. 1 out of 4 operated at 7-10 years moved up in height and out of 5 operated at 11 years or over only 2 moved upwards while 1 went downwards in weight percentile. The mean systolic pulmonary arterial pressure showed the greatest postoperative reduction in the youngest operated group (Table 18).

Table 18. *Systolic pulmonary arterial pressure before and after surgery according to the age at operation. PDA+PH group, boys*

Age at operation years	Preop. systolic PA pressure: Number of patients	Range (mm Hg)	Mean (mm Hg)	Postop. systolic PA pressure: Number of patients	Range (mm Hg)	Mean (mm Hg)
	4 (3)	78-115	93.8 (93.3)	3	35-55	42.7
7-10		55-100	73.0	4	26-60	44.3
11	5	73-100	91.6	5	42-84	71
Total	13 (12)	55-115	86.5 (85.8)	12	26-84	55.3

Figures in parentheses are the preoperative mean systolic PA pressure of the boys (number in parentheses) who were catheterized postoperatively

Effect of additional factors. The group of boys with PDA+PH included 3 prematurely born, all of whom were below the 50th percentile of height pre- and postoperatively. In weight they were all below the 2.5th percentile before surgery and after surgery 3 boys were still in this channel and the fourth boy had moved upwards to the 2.5–16 channel. Boys with an extracardiac congenital anomaly (3) or with close relations affected with congenital anomalies (1) did not differ from the rest of the group (Tables 2 and 3).

Girls (42 cases, Table 19)

Height and weight growth. The preoperative mean height value (876.43) and weight value (819.29) were highly significantly below normal. About a year after surgery (average 1 year 6 days, 1.02 year) the mean height (931.12) continued to be significantly and the mean weight (916.5) highly significantly under the normal.

When these measurements are fitted into the percentile curves of the Finnish child growth study it is found that the greater part of the

Table 19 *Results of girls in the PDA + PH group (4 cases)*

	[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Preop	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Postop	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]	

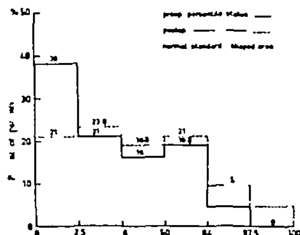


Fig. 7 Girl with patent duct s arteriosus with pulmonary hypertension. Compariso f height perc ntile stat distribution befor and after surgery w th normal standard for I innish hildren (12 16)

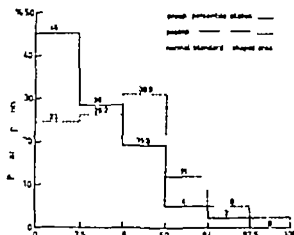


Fig. 8 Girls with patent ductus arteriosus with pulmonary hyperte sion. Comparison f weight percentile status distribution before and after surgery with normal standard for I innish childr n (12 16)

(59.5 per cent in height and 13 8 per cent in weight) were preoperatively below the 16th percentile Some acceleration in growth occurred postoperatively but there still remained in this channel 45.. per cent with respect to height and 50 0 per cent with respect to weight (Figs. 7 and 8). The greatest individual deviations in pre operative height and weight were slightly more than 3 SD and the greatest individual post operative acceleration was somewhat more than +1 SD in height and slightly more than 2 SD in weight. The preoperative mean height value was 1.. SD and the weight value 1 8 SD and the mean postoperative increases were respectively 0.5 SD and +1 SD from these values.

Physical capacity was reduced in 37 girls before operation and in 3 of these after operation, the mean values of the group being 1 and -0 07 respectively

Predisposition to infectious diseases was present in 25 girls preoperatively and in 1 girl post operatively giving group means of 0 60 and 0 0 respectively

Congestive heart failure w diagnosed prior to surgery in 11 girls with PDA+PH in the young est operated group and in no case after surgery

Pulse pressure was mean 62 mm Hg pre oper tively and 36 mm Hg postoperatively

The mean *systolic pulmonary arterial pressure* was preoperatively 69 9 mm Hg. The 26 patients catheterized postoperatively showed a decrease to mean 43 0 mm Hg, the smallest reduction was 12 mm Hg. The mean preoperative pressure of these 6 patients was 82 1 mm Hg, i.e. higher than that of the entire group In the 16 girls on whom catheterization was not performed after operation the signs of pulmonary arterial pressure reduction were distinct clinically

Preoperative *electrocardiography* revealed right ventricular hypertrophy in all the girls with PDA PH with a mean value of 1 12. Following surgery the mean was 0.34 9 girls still exhibiting hyper trophy

Left ventricular hypertrophy was present in 33 patients before and in 13 after operation. The group means were 1 93 and 0.56 respectively

Heart size was larger than normal before operation in all patients in this group, and in 22 cases remained larger than the normal for the age The preoperative group mean of 2.29 decreased after operation to 0.76. The relative heart volume decreased after surgery from 594 7 to 400 0 ml/m^2 BSA

Effect of age at operation (Table 20). Distribution of the girls with PDA+PH by age at operation into groups under 7 years (23 girls) 7 10

Table 20. *Effect of age at operation. PDA + PH group, girls (42 cases)*

Age at operation ⟶	1. < 7 years (23 girls) Mean	SD	2. 7 10 years (11) Mean	SD	3. 11 years (8) Mean	SD	p between groups 1 2	1 3	2 3
Preoperative height	839.61	156.86	931 82	88 45	906 13	142 41	0.05		
weight	775 65	146.24	873 73	79.20	869.88	86 33	0 01	0 05	
physical capacity	1 13	0.55	−0 91	0.54	1 38	0.74			
predisp. to infections	0.61	0.50	0.55	0.52	0 63	0.52			
RVH	1.04	0.82	1.00	0.89	1.50	0.93			
LVH	2.09	0 73	1 91	0.83	1.50	0 93			
heart volume ml/m² BSA	565.39	103.80	558 18	118.31	723.50	185.50		0 05	0.05
Postoperative height	920.74	183.33	971.00	92.38	906.13	142.40			
weight	916.74	142.63	938 73	80.99	885.38	86.81			
physical capacity	0 00	0 00	0.09	0.30	−0.25	0 46			
predisp. to infections	0.04	0.21	0.00	0.00	0 00	0.00			
RVH	0.14	0.35	0.55	0 69	0 63	0.74	0.05	0 05	
LVH	0.36	0 66	0 82	0 87	0.75	0 71			
heart volume ml/m² BSA	358.70	85.56	396 00	55.22	523 75	103.22		0 001	0 01

not significant

years (11), and 11 years or over (8) shows that the greatest acceleration in height and weight occurred in the youngest group after operation. The post-operative physical capacity was normal in all cases in this group reduction in heart volume was the most clear, and the mean systolic pressure of the pulmonary artery was lowest (Table 21) Thus the greatest benefit from the operation was seen in this group.

Effect of additional factors (Tables 2 and 3) When examining separately those girls who had been born prematurely (10 patients) those in whom extracardiac congenital anomalies had been found (9 with one, 1 with two anomalies) and those among whose close relations congenital anomalies had been diagnosed (4 patients) it will be observed that 8 of the 10 prematurely born girls were below the 2.5th percentile in height and weight, and all 10 were below the 50th percentile in height and the 16th percentile in weight Post operatively 7 of the 10 were still below the 16th percentile in both height and weight and 9 were below the 50th percentile The girls who had been born prematurely were thus in lower growth channels than the rest of the group of PDA PH girls, whereas the other additional factors studied were not found to influence height and weight growth.

Table 21 *Systolic pulmonary arterial pressure before and after surgery according to the age at operation. PDA PH group, girls*

Age at operation, years	Preop. systolic PA pressure: Number of patients	Range mm Hg	Mean mm Hg	Postop. systolic PA pressure: Number of patients	Range mm Hg	Mean mm Hg
7	23 (13)	32 [illegible]	67 (77 [illegible])	13	20-41	30 0
7 [illegible]	11 (6)	55 119	75 0 (84 0)	6	25 72	52 0
≥11	8 7	39 125	86 1 (90 1)	7	23-48	33 7
Total	42 26)	35 123	69 9 (82 1)	26	20-48	42 9

Figures in parentheses are the preoperative mean systolic PA pressure of the girls (number in parentheses) who were catheterized postoperatively

Comparison between boys and girls (Table 22)

Preoperatively the mean height and mean weight values of boys with PDA+PH differed less from the normal than those of similarly affected girls. The differences between the two sexes were not, however statistically significant.

Following surgery the girls showed greater acceleration of both height and weight growth than boys. A year after operation the mean height and weight values were slightly higher in girls than boys, but the differences were not significant even at this time.

Preoperative right ventricular hypertrophy was

Table 22. *Comparison between boys (13 cases) and girls (42 cases) in the PDA + PH group*

	Height Preop	Height Postop	Weight Preop	Weight Postop	Physical capacity Preop	Physical capacity Postop	Predisp. infections Preop	Predisp. infections Postop	[illegible] Preop	[illegible] Postop	Syst. PA pressure Preop	Syst. PA pressure Postop	RVH Preop	RVH Postop	LVH Preop	LVH Postop	Heart vol. Preop	Heart vol. Postop	Heart vol. ml/m² BSA Preop	Heart vol. ml/m² BSA Postop	[illegible]
Boys	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Girls	[illegible]	[illegible]	[illegible]	[illegible]	−1 12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
p											[illegible]	[illegible]	[illegible]	[illegible]							

almost significantly more marked in boys than in girls, and boys had a significantly more elevated systolic pulmonary arterial pressure One year postoperatively the right ventricular hypertrophy and the systolic pulmonary arterial pressure continued to be almost significantly higher in boys.

In other respects no differences were found between the sexes.

Correlations between the various factors (Table 23)

The correlation before and after surgery were studied by means of correlation coefficients. Pre operatively left ventricular hypertrophy correlated almost significantly with height retardation but not with weight retardation. The other factors studied were not found to be notably correlated with height or weight growth either before or after operation.

Concerning correlation between the various factors it was found that preoperatively the physical capacity of the PDA+PH patients with predisposition to infectious diseases was almost significantly poorer than that of the non-predisposed patients. A significant correlation was seen between right ventricular hypertrophy and systolic pulmonary arterial pressure

It is also seen in the table that the more distinct the left ventricular hypertrophy preoperatively the better the physical capacity post operatively ($p < 0.01$) and the lower the post operative systolic pulmonary arterial pressure ($p < 0.001$).

Summary of results in the PDA + PH group

The PDA+PH group is comprised of 42 girls 13 boys, the ratio thus being 3 2 1

Some type of congenital anomaly had been diagnosed among the close relations of 7 7 per cent of the boys and 9.5 per cent of the girls, the total incidence being 9 1 per cent (Table 2)

The mother of one boy had had rubella infection in the third month of pregnancy the incidence of maternal rubella in the whole group was thus 1.8 per cent (Table 2)

Of the 52 patients whose birth weight was known, 25 per cent of both boys and girls were prematurely born (Table 2)

Extracardiac congenital anomalies had been diagnosed in 23 1 per cent of boys and 23.8 per cent of girls, or in 23 6 per cent of the group (Table 3)

The mean age of boy at the time of diagnosis of the congenital heart d fect was 2 2 years and f girl 1 8 years (Table 4)

The ag t operatio varied from 0 3 to 15 8 years, mean 7 0 years (Table 7)

The patent ductus was closed by ligation in 14 instances, by division in 37 instances, and by means of bulldog forceps in 4 instances (Table 8).

Six cases of recanalization occurred within the period of the present study The recanalization incidence thus was 10.3 per cent of the PDA PH group and 35.3 per cent of the ductus closures by ligation in this group In calculating these percentages there are included in the group in addition to the original 55 patients, 3 who had been excluded because of incomplete data (Table 9)

Surgical mortality was 11.8 per cent in boys and 8.5 per cent in girls, total 9 4 per cent, calculated as above (Table 10).

Preoperatively the mean height and weight values of boys with PDA+PH were significantly and those of the girls highly significantly below normal Some acceleration occurred after operation nevertheless the boys mean height and weight continued to be, a year after operation, almost significantly below normal and the girls mean height significantly and weight highly significantly below normal. In both sexes weight was more retarded than height as well before as after surgery

Before operation the mean height and weight of girls were more greatly retarded than those of boys, but following surgery they showed more marked acceleration of both height and weight growth than the boys, so that postoperatively the boys were more retarded than the girls in both respects. The differences between sexes were not significant either before or after surgery

The greatest acceleration in height and weight growth was seen in the group of patients operated on at the earliest age i.e. under 7 years.

Following surgery the mean physical capacity of the patients improved, predisposition to infectious diseases decreased, pulse pressure declined, systolic pulmonary arterial pressure fell, ECG signs of right and left ventricular hypertrophy diminished and heart size decreased.

It was found that the higher the pulmonary arterial pressure, the more marked the right ventricular hypertrophy and the reduction of physical capacity On the other hand, the more marked the preoperative left ventricular hyper trophy was, the lower was the postoperative systolic pulmonary arterial pressure and the better the physical capacity

Discussion

In the period from April 1958 to April 1967 a total of 64 operations were performed on the

Table 22 (3) Correlation coefficients in the PDA PH group (55 patients)

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 1)	17	18	19	20	21
Preoperative height	1	999																				
weight	2	838	999																			
physical capacity	3	052	306	999																		
predisposition to infections	4	008	008	80	999																	
systolic PA pressure	5	333	50	334	165	999																
pulse pressure	6	229	305	180	010	237	999															
RVH	7	016	011	265	072	422	100	999														
LVH	8	84	255	129	065	198	134	048	999													
heart size	9	006	108	095	062	329	445	063	348	999												
volume ml/m2 BSA	10	101	168	113	014	138	248	115	319	615	999											
Diameter of ductus	11	071	057	138	081	119	160	077	02	086	184	999										
Postoperative height	12	832	711	064	111	125	110	019	205	089	028	095	999									
weight	13	814	814	194	068	006	120	121	232	106	053	120	881	999								
physical capacity	14	220	230	367	071	425	235	177	4 5	144	175	028	149	030	999							
predisposition to infection	15	-015	071	021	120	008	250	122	024	146	012	189	245	116	018	999						
1) systolic PA pressure	16	389	400	? 6	-051	689	417	199	596	647	320	413	188	054	557	209	999					
pulse pressure	17	129	109	007	099	011	252	000	091	034	064	112	144	005	161	098	221	999				
RVH	18	219	265	152	006	321	345	574	193	359	078	049	107	042	349	089	565	221	999			
LVH	19	091	051	158	101	020	119	252	457	114	286	003	208	273	105	108	054	129	287	999		
heart size	20	362	326	190	063	137	115	012	143	335	545	224	222	328	100	039	081	217	051	141	999	
volume ml/m2 BSA	21	474	533	094	032	325	043	127	156	139	634	458	308	301	190	044	435	111	204	116	821	999

1) Measured in 38 cases

	For 55 observations	For 38 observations
p 0.05	266	320
0.01	345	413
0.001	432	513

Significant correlations are underlined

diagnosis of patent ductus arteriosus with pulmonary hypertension in the Children's Hospital, University of Helsinki In the same period 477 operations were made for uncomplicated patent ductus. Thus, of all the cases of patent ductus corrected surgically in this period 11.8 per cent were complicated with pulmonary hypertension. This incidence agrees well with the findings in other statistics, in which it varies between 5 and 17 per cent (54 147 147 159) though an incidence as high as 35 per cent has been reported (8)

Comparison of the PDA and the PDA+PH groups shows that the disease was considerably more severe in the latter with respect to all the symptoms and objective findings (Tables 24 25 6)

Twenty five per cent of the patients with PDA+PH had been prematurely born, which is a considerably higher incidence than that in the general Finnish population in the period studied (5 per cent, 139 140) Krovetz and his co-workers reported in 1962 (97) that 41 per cent of patients with patent ductus operated on when under 1 year of age were prematures, whereas there were 11 per cent among those submitted to surgery at over 1 year of age. Other series contain in general an above normal proportion of prematurely born patients with patent ductus, those with pulmonary hypertension not being stated separately (11 95 98 109 116).

Extracardiac congenital anomalies had been diagnosed in 23 6 per cent of patients in this group. This is slightly more than in the study of Boesen and his co-workers, in which 18.2 per cent of PDA patients with systolic pulmonary arterial pressure over 40 mm Hg had also extracardiac congenital anomalies (26). These anomalies have been reported in general in 12 20 per cent of patients with open ductus (9 11 26 78, 98 170)

The findings concerning growth in the PDA+PH group correspond to those in other series. Before surgery there was considerable retardation of height and weight, as has been observed in all studies in the literature In the few cases of PDA + PH for which postoperative growth data are reported there was definite acceleration of growth (159)

Mean postoperative acceleration of height and weight growth was greatest in the group operated on at the earliest age. This group showed also the most distinct decrease in mean systolic pulmonary arterial pressure.

Preoperatively the boys were slightly in advance of the girls in mean height and weight. On the other hand, the postoperative acceleration in both height and weight was greater in girls, and consequently boys were slightly more retarded than girls a year after operation. The greater postoperative benefit from surgery in the girls group is understandable in view of their earlier age at operation and the lower preoperative mean systolic pulmonary arterial pressure.

The criterion of the PDA+PH was a systolic pulmonary arterial pressure over 50 mm Hg. Comparison with other studies is difficult since their criteria have varied between 30 and 60 mm Hg and the groups studied have been small. In the opinion of Anabtavi and co-workers (8), a

Table 4 *Comparison between boys in the PDA group (?7 cases) and in the PDA + PH group (13 cases)*

	Height		Weight		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	[illegible]
PDA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]		[illegible]	[illegible]	[illegible]
PDA+PH	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
					[illegible]	[illegible]					[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Table 25 *Comparison between girls in the PDA group (73 cases) and in the PDA + PH group (42 cases)*

	Height		Weight		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	[illegible]
PDA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
PDA+PH	[illegible]		[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]					[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Table 26 *Comparison between the PDA group (100 cases) and the PDA + PH group (55 cases)*

	Height		Weight		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	[illegible]
PDA	[illegible]	[illegible]	[illegible]			[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
PDA+PH	[illegible]	[illegible]					[illegible]			[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]									[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

systolic pressure over 60 mm Hg does not generally become normalized even after a successful operation. On the other hand, some excellent falls in pressure have been reported. Adams (3) described the case of a 15-year-old girl whose systolic pulmonary arterial pressure dropped within a year after operation from 100 mm Hg to 40 mm Hg. Berlind and co-workers (22) and Siber with his co-workers (158) have each presented a group of 4 patients with systolic pulmonary arterial pressure over 90 mm Hg before surgery and a fall in all cases to 21–60 mm Hg, though a fully normal level was reached only by one patient in each group.

A preoperatively elevated pulmonary arterial pressure was observed by Krovetz (95) to have an unfavourable effect on the preoperative body weight but not on the height or on the postoperative height and weight. In the present study the systolic pulmonary arterial pressure was not found to influence height or weight growth either before or after surgery.

In this work a correlation was found between the mean systolic pulmonary arterial pressure, right ventricular hypertrophy and reduced physical capacity both before and after operation.

On the other hand the observation was made in the PDA + PH group the degree of preoperative left ventricular hypertrophy had an inverse correlation with postoperative systolic pulmonary arterial pressure and physical capacity. In other words, preoperative LVH was a good prognostic sign of the patient's postoperative condition, although, on the other hand, LVH had before operation an almost significantly unfavourable correlation with preoperative height, but not with preoperative weight or with postoperative height and weight growth.

There has everywhere been a continuous reduction in the age at which surgery is undertaken on patients with a symptomatic patent ductus. Probably the youngest surgical patient is the 2-day-old newborn successfully operated on by Joly and his co-workers (81). Surgical treatment is recommended today as soon as possible after onset of symptoms as possible since this will give the most favourable effect on height and weight growth and on pulmonary arterial pressure as well as on other symptoms and signs (60, 61).

Surgical mortality in the PDA+PH group was 9.2 per cent, corresponding to values ranging from 0 to 42 per cent reported in the literature (142, 147). Grouped according to sex the surgical mortality among boys (11.8 per cent) was clearly higher than that among girls (8.5 per cent). In examining the records of their hospital on patients operated on for patent ductus during a period of 20 years Krovetz and Warden (98) observed a twice as high surgical mortality among males as among females.

Coarctation of the aorta (Co)

Boys (78 cases, Table 27)

Height and weight growth. The preoperative mean height value (976.06) was almost significantly and the mean weight value (974.45) significantly below the normal expressed as 1000. About one year after operation (mean 1 year 6 days = 1.02 year) the mean height (991.41) and mean weight (989.45) did not differ from the normal.

From the graphs in which the boys with Co are fitted into the percentiles of the Finnish child growth study group (Figs. 9 and 10) it is seen that before surgery a slightly greater than normal proportion of the boys were in the two lowest channels of height and weight. After surgery the distribution was very close to normal. The largest individual deviation preoperatively was about −2 SD in both height and weight. Postoperatively the greatest individual catch-up in height was slightly less than +1 SD and in weight slightly over + 1.5 SD. The height and weight growth values of 3 boys in the oldest age group (11 years and over) were, however about 0.5 SD lower than their own preoperative values. The mean height of the whole Co group preoperatively was −0.2 SD and the mean weight −0.3 SD and the mean postoperative catch-up was +0.1 SD in height and slightly less than + 0.2 SD in weight.

Physical capacity was reduced in 45 boys before surgery, the group mean being −0.64. After surgery the physical capacity of 2 boys

Table 27 *Results of boys in the coarctation group (78 cases)*

	Height		Weight		Physical capacity		[illegible]		Syst. blood pressure		RVH		VH		[illegible]		[illegible]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Preop.	976.06	94.06	974.45	97	−0.64	0.53	18	[illegible]		0.53	0.22	0.60	60	[illegible]	0.76	71	[illegible]	[illegible]
Postop.	[illegible]	[illegible]	[illegible]	84	−0		0.00	[illegible]	33		0.3	[illegible]	43	0.3	0.1	0.43	[illegible]	1.52
p					< 0.00		< 0.001		< 0.001		< 0.01		< 0.001		ns		< 0.01	

ns significant



Fig. 11 G ls with coarctation of the aorta. Comparison of height percentile status distribution before and after surgery with normal standard for Finnish children (12 162)

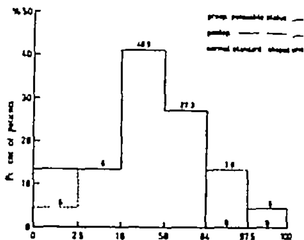


Fig. 1.. Girls with coarctation f the aorta. Comparison of weight percentile status distribution before and after surgery with normal tandard for Finnish children (12, 162)

Predisposition to infectious diseases was found in the preoperative history of 7 girls and post operatively in one of these.

Congestive heart failure was present before operation in 2 girls in the youngest group and one girl operated on at a later age had had this condition in infancy

Systolic blood pressure (Table 31) was elevated before operation in all patients with the exception of an infant subjected to surgery at the age of 3 months. The mean value was 1 73 This fell postoperatively to 0 41 the blood pressure having decreased in all of the girls with the exception of one in whom recoarctation had developed during the observation year Nevertheless the systolic blood pressure after surgery was still elevated in nearly half of the girls.

Electrocardiography showed signs of right ventricular hypertrophy preoperatively in 5 girls and postoperatively in 1 girl, the mean degree of hypertrophy being 0.27 and 0 05 respectively

Left ventricular hypertrophy was present before surgery in 20 girls and after surgery in 9 with group means of 1.64 and 0 45 respectively

Heart si.e was larger than normal for the age in 13 girls preoperatively and in 7 of them post operatively the mean size being 0.91 and 0.27 respectively The hearts of 2 girls decreased in size after surgery although they had been within normal limits before surgery

T ble 31 *Systolic blood pressure (mm Hg) before and fter surgery by age at operation Co girls*

Age at oper years	No. of patients	Preoperat ve Mean	Range	Postoperat Mean	Range	Postoperative > 120 mm Hg No. of patients	%
7	5	147	120-170	127	110-165[1]	1	20.0
7 10	10	157	140-180	120	110-130	3	30 0
11	7	169	150-240	131	115 140	5	71 4
T tal	22	159	120-240	125	110-165	9	40.9

1) Whe one infant with recoarctation and blood pressure 165 mm Hg is excluded, the range in the youngest age group w ll be 110-120 mm Hg, the mean 115 mm Hg, and the mean of the Co girls group 122 mm Hg, and post-operat vely 8 girls will have blood pressure more than 120 mm Hg, i.e 36 4 %

Table 32 Effect of age at operation. Co group, girls (cases)

[illegible]operation →	1. 7 years (5 girls) Mean	SD	2. 7 10 years (10) Mean	SD	3. 11 years (7) Mean	SD	p between groups 1 2	1 3	2 3
Preoperative height	825.40	169.54	989.60	69.64	974.57	109.05	0.01	<0.05	
weight	804.00	281.51	977.00	63.57	985.14	66.06			
physical capacity	1.40	0.55	-0.70	0.48	-0.57	0.53	0.05	<0.05	
predisp. to infections	0.80	0.45	0.10	0.3	0.79	0.49	0.01	<0.05	
RVH	0.80	0.84	0.20	0.63	0.00	0.00		<0.05	
LVH	2.00	1.00	1.50	0.97	1.57	0.53			
heart size	2.20	0.84	0.50	0.71	0.57	0.53	0.00	<0.001	
heart volume ml/m² BSA	466.00	156.78	392.00	69.25	390.00	52.44			
Postoperative height	921.40	128.79	1014.00	66.61	976.14	94.25	<0.05		
weight	937.60	188.42	1008.60	78.84	990.57	74.10			
physical capacity	-0.70	0.45	0.00	0.00	0.00	0.00			
predisp. to infections	0.70	0.45	0.00	0.00	0.00	0.00			
RVH	0.20	0.45	0.00	0.00	0.00	0.00			
LVH	1.00	0.71	0.40	0.70	0.14	0.38		<0.05	
heart size	0.60	0.55	0.10	0.32	0.29	0.49	0.05		
heart volume ml/m² BSA	360.00	58.31	373.00	41.38	390.00	73.26			

not significant

Effect of age at operation (Table 32) Comparison between the three groups distributed according to age at operation, i.e. 5 girls under 7 years, 10 girls 7 10 years, and 7 girls 11 years or over, shows that before operation the mean height value in the youngest group was significantly lower than that in the middle group and almost significantly lower than that in the oldest group the mean weight value was almost significantly lower in the youngest group than in the middle group The greatest deviations from normal in also other respects were seen in the youngest group The heart in particular showed the most marked enlargement in relation to age in this group the difference from the other age groups being highly significant. The postoperative changes towards normal were most clearly evident in the youngest group, although the mean height value remained almost significantly lower than that of the middle group. The mean weight value likewise was the lowest, but the differences were not statistically significant.

Additional factors, i.e. prematurity (1 girl) extracardiac congenital anomalies (1 girl) and congenital anomalies in close relations (3 girls, Tables 2 and 3), were not found to have influenced the height and weight growth of girls with Co

Comparison between boys and girls (Table 33)

Comparison between boys and girls (Table 32). A comparison between the boys and girls with Co shows that girls were slightly though not statistically significantly lower in mean height and mean weight values both before surgery and about a year later Neither were any significant differences found between the se es with respect to physical capacity predisposition to infectious diseases, congestive heart failure blood pressure ECG findings or heart size

Correlations between the various factors (Table 34)

Preoperatively congestive heart failure, right ventricular hypertrophy and enlargement of heart were highly significantly correlated with weight retardation and almost significantly with height retardation. Predisposition to infectious diseases had before surgery a significant correlation with both height and weight retardation. Preoperative congestive heart failure had an almost significant inverse correlation with postoperative height

Table 33 Comparison between boys (78 cases) and girls (22 cases) in the Co group

	Height Preop	Postop	Weight Preop	Postop	Physical capacity Preop	Postop	Predisp. to infections Preop	Postop	Syst. blood pressure Preop	Postop	RVH Preop	Postop	LVH Preop	Postop	Heart size Preop	Postop	Heart vol/m² BSA Preop	Postop
Boys	[illegible]	[illegible]	[illegible]	[illegible]	-0.44	-0.43	[illegible]	[illegible]			23	[illegible]	68	43	76	27	36.75	[illegible]
Girls	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	73		[illegible]	[illegible]	64	45			15.00	[illegible]

not significant

Tabk 34 *Correlation oeffice ts in th coarctation group (100 patients)*

		1	2	3	4	5	6	7	8	9	10[1]	11	12	13	14	15	16	17	18	19[2]
Preope tive height	1	999																		
ight	2	286	999																	
phy ical capac ty	3	150	.9.	999																
predisposition t infection	4	.84	.8.	395	999															
ongestive heart f ilure	5	.97	447	290	176	999														
ystolic blood pressur	6	.11	134	087	057	045	999													
RVH	7	.38	438	.87	161	444	054	999												
LVH	8	204	177	199	165	050	152	.45	999											
heart size	9	287	394	.86	.57	459	015	698	.66	999										
1) volume ml/m^2 BSA	10	170	210	106	088	218	059	593	289	839	999									
Postoper tive height	11	915	676	075	145	217	.2.	145	148	149	111	999								
weight	12	708	826	105	149	.15	.09	.17	157	180	134	718	999							
physical apacity	13	038	114	350	.13	038	002	.31	118	257	.73	110	019	999						
predisposition t infection	14	..3	.66	304	341	127	061	5.9	.7.	501	413	099	096	416	999					
systolic blood pressu	15	060	058	002	116	070	180	017	016	015	054	167	155	012	068	999				
RVH	16	053	060	.4.	213	20.	001	5.3	304	366	413	.28	174	0 1	.65	1 8	999			
LVH	17	080	042	190	204	040	082	065	575	185	194	046	040	.13	.59	078	.86	999		
he t siz	18	184	090	149	161	045	050	.34	300	510	5..	054	003	290	4.6	019	289	291	999	
2) volume ml/m^2 BSA	19	055	223	016	063	.80	110	046	202	.13	458	127	182	404	2.8	123	236	323	743	999

1) Det rmined in 94 cases
2) in 96

For 100 observations,		for 94 observ tions,	for 96 observation
p <0.05	197	203	201
<0.01	257	265	262
<0.001	324	334	331

Significant correlations are underlined

and weight values. The other factors studied were not found to have any noteworthy correlation with height and weight growth.

It also appears from the table that preoperative congestive heart failure, right ventricular hypertrophy and enlargement of heart were mutually correlated at a highly significant level.

Summary of results in the coarctation group

This group was comprised of 100 consecutive patients with uncomplicated coarctation of the aorta. There were 78 boys and 22 girls, the sex ratio being 3.5 1

In the close relations of 6 4 per cent of the boys, and 13.6 per cent of the girls, i.e 8.0 per cent of the whole group there was some congenital anomaly (Table 2).

Among the 93 patients whose birth weight was known there were no cases of prematurity among the boys and one case among the girls (Table 2)

An extracardiac congenital anomaly had been diagnosed in 7 7 per cent of the boys and 4.5 per cent of the girls, or in 7.0 per cent of the Co group (Table 3).

The mean age at diagnosis of the congenital heart disease was 5 9 years in the boys group and 4 4 years in the girls group. About half of the cases had been detected at routine medical examinations (Table 4)

The age at operation varied from 0.3 to 15.8 years, mean 8 7 years (Table 7)

Operative mortality in all surgically treated cases of Co in the period studied was 10.3 per cent among boys and 7 7 per cent among girls, when girls with Turner s syndrome were excluded the latter incidence was 4.3 per cent (Table 10)

Preoperatively the mean height and weight of both boys and girls with Co were below normal. Weight was more greatly retarded than height and the girls slightly more than boys. One year after surgery the mean height and weight no longer differed from normal in either sex, but girls values were slightly below those of boys. Also now the boys' mean value for weight was slightly lower than that for height, whereas in girls the height was slightly low than the weight

The most marked postoperative acceleration in both height and w ght growth was found to occur in the group of patients operated on t the earliest age (under 7 years).

Following surgery the patients mean physical capacity improved, predisposition to infectious diseases decreased, blood pressure declined, hypertrophy shown by the ECG diminished, and the heart decreased in size

Preoperatively the systolic blood pressure was above normal for the age in all patients with the exception of one infant A year after operation this girl was found to have developed recoarctation with elevated blood pressure. In all the other cases the systolic blood pressure was reduced from the preoperative level, although in about one-third the systolic pressure remained slightly or moderate above normal for the age

The group of Co patients submitted to surgery at the earliest age exhibited the most symptoms preoperatively and surgery was of the best benefit to the subjective condition as well as to the objective signs in this group

Discussion

The group of patients with coarctation of the aorta had a predominance of boys, as is known generally to be the case (1 36, 69 88 96 1‸6 143).

About a half of the cases had been detected at routine medical examinations. This corresponds well with the statement in the literature that the greater part ha e been diagnosed at routine examinations (36).

Extracardiac congenital anomalies had been diagnosed in 7 per cent of the patients with Co. This is a slightly lower incidence than for example, that found by Boesen and co-workers (26) in a similar clinical series, in which 10 per cent of children with coarctation of the aorta had extracardiac congenital anomalies. Autopsy series naturally ha e a higher incidence of congenital anomalies additional to Co (130).

Although the majority of these patients with Co had been considered to be healthy in all respects before surgery the preoperative mean height and weight of the group were below normal The operation was found to have had a favourable effect on both parameters, the mean height and weight being within normal limits a year after surgery This agrees well with the observations in studies in which the mean height and weight (121) or only the mean weight (58) were below normal preoperatively In both studies surgery was found to influence favourably both the mean height and the mean weight growth.

Prior to surgery a predisposition to infectious diseases, congestive heart failure and right ventricular hypertrophy were correlated with retardation of both height and weight growth. Preoperative congestive heart failure had also an almost significant inverse correlation with postoperative height and weight growth.

It is a general observation that boys with congenital heart disease are more retarded in

growth than girls with this condition (106). In the present group of patients with Co however the mean height and weight values of girls were lower both before and after surgery on the other hand the benefit from surgery was more distinct in girls.

Postoperatively the systolic blood pressure declined in all the patients with Co with the exception of an infant who developed recoarctation during the observation year. The systolic blood pressure remained, however elevated in relation to age in about a third of the patients, corresponding to the finding in other studies (141 152) even if series have been presented in which an above normal blood pressure persisted post operatively in only 10 per cent of cases (69 7).

Since postoperative acceleration of both height and weight growth was greatest in the youngest Co group (under 7 years) and least in the oldest age group (11 years and over), it is to be recommended that surgery for Co is performed before the age of 10 years, 7-8 years generally being considered to be the optimal age (61 122). Surgery can be life saving in some cases already in infancy when it should be performed in cases in which medical treatment does not bring about definite improvement in the patient s condition (31 61 12-, 123 128 134 160).

Surgical mortality was 9 1 per cent in all uncomplicated cases of coarctation (also excluding cases of Turner s syndrome) operated in this hospital during the period studied. Distribution by sex shows a higher surgical mortality among boys (10.2 per cent) than among girls (4 3 per cent).

Tetralogy of Fallot (TF)

Boys (62 cases, Table 35)

Height and weight growth. The preoperative mean height value (880 47) and mean weight value (855 44) were both statistically highly significantly below normal. About a year after operation (average 1 year 38 days = 1 12 year) the mean height (911.58) and mean weight (867.55) were still highly significantly below normal.

When these boys with TF are distributed into the percentile of the Finnish child growth study group (Figs. 13 and 14) over a half are found to be below the 16th percentile in both height (59 7 per cent) and weight (67 7 per cent) before surgery. Regardless of some acceleration postoperatively into higher channels, a half of the boys remained in the two lowest channels (in height 51.6 per cent, in weight 59.6 per cent). The

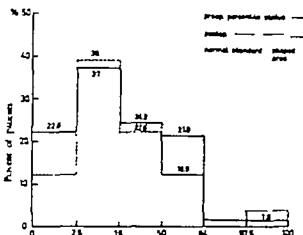


Fig. 13 Boys with tetralogy of Fallot. Comparison of height percentile status distribution before and after surgery with normal standard for Finnish children (12, 162)

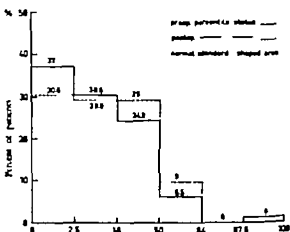


Fig. 14 Boy with tetralogy of Fallot. Comparison of weight percentile status distribution before and after surgery with normal standard for Finnish children (12, 162)

Table 35 *Results f boy wi th TF group (6 cases)*

	Height		Weight		Physical capacity		Tendency to infections		Hb		Hkr				Heart size		Heart vol ml/m² BSA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Preop	[illegible]	[illegible]	85 44	109 34	2.54	.54	0	0 49		[illegible]	[illegible]	11 02	1 83	76	33	0 42	[illegible]	[illegible]
Postop	[illegible]	[illegible]	[illegible]	[illegible]	−0 93	[illegible]	[illegible]	25	[illegible]	2 06	[illegible]	[illegible]	1 58	0 62	0 43	0 58	[illegible]	[illegible]
					[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]	

greatest individual deviation from the normal preoperatively was equal to 3 SD in both height and weight. Postoperatively the greatest individual acceleration was over +1 SD in both height and weight growth, however in the oldest age group 2 boys showed retardation of slightly less than 1 SD from their own preoperative values. The preoperative mean height of the boys with TF was 1.2 SD and weight 1.4 SD and the postoperative mean acceleration was +0.3 SD in height and +0.1 SD in weight.

Physical capacity was reduced preoperatively in all cases, the maximum reduction being −3. Postoperatively it was improved in all, though only 12 patients reached a fully normal level. The preoperative mean of 2.58 improved to −0.95 postoperatively.

Predisposition to infectious diseases was present in 23 patients before surgery and persisted in 4 after surgery.

Signs of *congestive heart failure* were not seen in any of the patients at the time of operation, but 2 of the boys had shown signs of this condition in infancy.

Cyanosis, haemoglobin and haematocrit. Before surgery all the boys with TF were cyanotic at rest and the Hb concentration varied between 14 and 25 g/100 ml, mean 18.2 g/100 ml. Postoperative values were 13-23 g/100 ml, mean 16.1 g/100 ml.

Preoperative Hcr determination in 53 boys gave values of 43-83 ml/100 ml, mean 59. Postoperative determinations were made in 46 boys, with values of 40-72 ml/100 ml, and mean 51.

Electrocardiograms showed signs of right ventricular hypertrophy in all cases before surgery, the mean degree of hypertrophy was 1.85. After operation it was still present in all the boys but slightly less severe, the mean being 1.50.

Left ventricular hypertrophy was not seen in any case either before or after surgery, even if the left ventricular potentials were better evident at the latter time.

Heart size was preoperatively larger than normal for the age in 14 boys. After surgery it was reduced in 4 of them and remained almost unchanged in 10. These 14 boys did not differ from the rest of the group with respect to age at operation, physical capacity or laboratory test results. The mean heart size of the boys with TF increased after surgery to 0.63 from the preoperative mean value of 0.23.

Effect of age at operation (Table 36). When the boys are divided into three groups by age at operation, i.e. 31 boys under 7 years, 19 boys 7-10 years, and 12 boys 11 years or over, the middle group shows the least difference from the normal height and weight pre- and postoperatively. The greatest retardation both before and after surgery was seen in the youngest group with respect to height, but with respect to weight in the oldest group, in which the mean weight was postoperatively slightly retarded further from its preoperative value. The greatest acceleration in mean weight growth after surgery occurred in the youngest group, while acceleration in height growth was somewhat greater in the middle group than in the youngest group. The mean height value of the middle group was both pre- and postoperatively almost significantly higher than that of the youngest group, while postoperatively its mean weight value was almost significantly higher than that of the oldest group. Other differences in

Table 36. *Effect of age at operation. TF group, boys (62 cases)*

Age at operation →	1 < 7 years (31 boys) Mean	SD	2 7-10 years (19) Mean	SD	3 ≥ 11 years (12) Mean	SD	p between groups 1 2	1 3	2 3
Preoperative height	850.03	133.16	926.89	127.15	885.58	90.79	0.05		
weight	841.61	97.48	892.42	132.70	832.58	92.62			
physical capacity	2.43	0.41	2.84	0.36	2.58	0.49	<0.50		
Hb	18.10	2.98	18.32	2.96	18.25	2.22			
RVH	1.71	0.74	2.11	0.74	1.83	0.83	<0.05		
heart size	0.23	0.43	0.16	0.37	0.33	0.49			
heart volume ml/m² BSA	320.60	48.48	341.43	65.97	413.75	73.08		<0.001	
Postoperative height	881.45	124.83	974.42	162.12	889.92	91.66	<0.05		<0.05
weight	864.29	102.21	899.21	130.23	825.83	91.84			
physical capacity	−0.96	0.64	1.60	0.46	−0.91	0.26			<0.05
Hb	15.94	2.19	15.95	2.64	16.58	1.83			
RVH	1.39	0.50	1.58	0.69	1.67	0.78			
heart size	0.65	0.61	0.53	0.61	0.75	0.45			
heart volume ml/m² BSA	371.43	47.51	407.33	67.13	456.67	49.50	0.05	<0.001	<0.05

not significant

Table 37 *Results of girls in the TF group (38 cases)*

	Height Mean	Height SD	Weight Mean	Weight SD	Physical capacity Mean	Physical capacity SD	Tendency to infections Mean	Tendency to infections SD	Hb Mean	Hb SD	Hkr Mean	Hkr SD	RVH Mean	RVH SD	Heart size Mean	Heart size SD	Heart vol. ml/m2 BSA Mean	Heart vol. ml/m2 BSA SD
Preop	933 1	138 [illegible]	889 53	34 56	-2 3	47	37	0 49	18 7	3 60	1 56	34 3	1 79		13	0 1	3 79	81 34
Postop	963	117 95	910 16	96 75	-0 75	40	00	00	1 08	2 40	51 26	6 06	1 9	50	2	64	377 50	64 63
p						001		001		001		01		05		05		01

not significant

height and weight values were not statistically significant.

Right ventricular hypertrophy before surgery was almost significantly more marked in the middle group than in the youngest group. There were no notworthy significant differences between the age groups in other respects either before or after palliative surgery

Effect of additional factors. Some additional factor was present in 25 cases, i.e. prematurity (7 boys) extracardiac congenital anomaly (14 boys) or congenital anomalies in close relations (7 Tables 2 and 3) Seven boys were prematurely born and 42 9 per cent of them were below the 2.5th percentile in height and weight before operation. A year after surgery none of these were below the 2.5th percentile in height, but 28.6 per cent had remained below this percentile in weight.

Of these 25 boys with one of the above factors in addition to TF there preoperatively were below the 2.5th percentile 28 per cent in height and 44 per cent in weight and postoperatively 17 per cent and 28 per cent, respectively Of the remaining 37 boys with TF whose history did not include any of these additional factors, 18 9 per cent in height and 35 1 per cent in weight were preoperatively below the 2.5th percentile and postoperatively 13.5 per cent and 32 4 per cent, respectively

In other words, in the presence of some additional factor the boys with TF were before surgery more frequently below the 2.5th percentile than the rest of the group, whereas after surgery they no longer differed from the others in this respect

Girls (38 cases, Table 37)

Height and weight growth. The preoperative mean height value (933 16) was significantly and the mean weight value (889.53) highly significantly below normal. About a year after surgery (average 1 year 94 days = 1.6 year) the mean height (963 97) was still almost significantly and the mean weight (910 16) highly significantly under the normal.

When distributed into the percentile tables of the Finnish child growth study group (Figs. 15 and 16) about half of the girls with TF were preoperatively below the 16th percentile (in height 44.8 per cent in weight 55.2 per cent) Following palliative surgery there was some shift into higher channels, but a larger than normal number remained in the two lowest channels in both

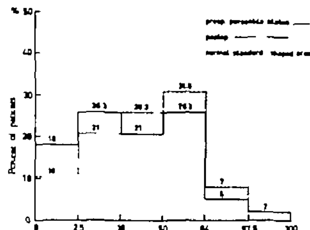


Fig. 15 Girls with tetralogy of Fallot Comparison of height percentile status distribution before and after surgery with normal standard for Finnish children (12, 16)

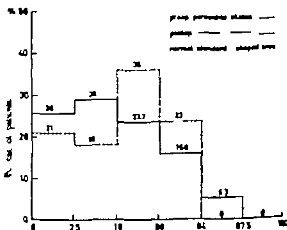


Fig. 16. Girls with tetralogy of Fallot. Comparison of weight percentile status distribution before and after surgery with normal standard for Finnish children (12, 162)

height (31.6 per cent) and weight (39.5 per cent). The greatest individual difference from the normal preoperatively was nearly 3 SD in height and over 3 SD in weight. The greatest postoperative acceleration was about + 1.5 SD in both height and weight growth, though 2 girls in the oldest age group dropped in weight more than 1 SD from their respective preoperative values. The preoperative mean height of the 38 girls with TF was -0 7 SD and the mean weight 1 1 SD and the postoperative acceleration was about + 0.3 SD in height growth and + 0.. SD in weight growth.

Physical capacity. Prior to operation the physical capacity of all the girls was low at the level of and 3 the mean being -..63. With one exception it improved after operation but became fully normal in 3 girls only. The lowest individual postoperative values were 2 and the mean was -0.95.

Predisposition to infectious diseases was found in 14 girls but disappeared after operation.

Congestive heart failure was not present in any of the girls with TF at the time of operation, although signs of this condition had been observed in infancy in 5 cases.

Cyanosis, haemoglobin and haematocrit. Preoperatively all the girls were cyanotic at rest. Hb varied between 13 and 6 g/100 ml, mean 18.5 g/100 ml, before surgery and between 13 and 23 g/100 ml, mean 16 1 g/100 ml after surgery.

Hcr determinations were made preoperatively in 31 cases; the values ranged from 45 to 94 ml/100 ml, mean 61.6. Postoperatively they were 43-76 ml/100 ml, mean 51.3 when determined in 27 cases.

Electrocardiograms showed right ventricular hypertrophy in all the patients, the mean degree of hypertrophy being 1 79 before surgery. It persisted after surgery in all cases but the mean degree was reduced to 1 45.

Signs of left ventricular hypertrophy were not evident either before or after operation.

Heart size before operation was larger than normal for the age in 4 girls with TF, the group mean was 0 13. Postoperatively the heart size decreased in of these 4 cases, in 1 case it was unchanged and in 1 case enlarged. The mean age of these 4 girls at the time of operation was 6 9 years (all girls with TF 7.5 years), their preoperative physical capacity was 75 (63) Hb 20.5 g/100 ml (18.5 g/100 ml) Hcr 71.8 ml/100 ml (61 6) and mean height and weight values approximately the same as those of the rest of the group. Following surgery these girls did not differ from the others in any of these respects.

About a year after operation the mean heart size of the group of girls with TF had increased from 0 13 to 0 4.

Effect of age at operation (Table 38). Comparison between the three age groups, i.e. 18 girls under 7 years, 10 girls 7 10 years, and 10 girls 11 years or over shows the lowest pre- and postoperative mean height and weight values in the group of girls operated on at the earliest age. On the other hand the greatest postoperative acceleration in growth occurred in this age group. Slight acceleration in the mean height growth was seen also in the other age groups, whereas the mean growth in weight was slightly retarded further in the middle and oldest age groups. Prior to surgery the youngest group had an almost significantly lower mean height value than the oldest group and a significantly lower mean weight value than the middle and oldest groups. Other differences between the age groups in height and

Table 38 *Effect of age at operation TF group, girls (38 cases)*

Age at operation →	1 < 7 years (18 girls) Mean	SD	2 7 10 years (10) Mean	SD	3 11 years (10) Mean	SD	p between groups 1 2	1 3	3
Preoperative height	896 06	114.67	948 10	179 76	985 00	123 47		<0.05	
weight	825 22	124 55	942.80	107 8	952 00	133 68	< 0 01	< 0 01	
physical capacity	2 72	0 45	2 60	1 07	2.50	0 50			
Hb	18 83	3 99	17 70	4 00	18 60	50			
RVH	1 56	0 70	2 40	0 52	1 60	0 70	0 01		< 0 01
heart size	0 17	0.51	0 10	0 32	0 10	0 41			
heart volume ml/m² BSA	270 71	58 90	300 00	60 33	392 50	75 34		< 0 001	< 0 05
Postoperative height	942 44	107 80	978 60	133 29	988 10	125 15			
weight	881 94	105 34	9..5 80	71..5	945 30	95 84			
physical capacity	-0 83	0 36	1 00	0 00	1 10	0 30		< 0 05	
Hb	16 72	2 99	15 40	01	15 60	1 07			
RVH	1.22	0 73	2 10	0 57	1 70	0.79	< 0 01		< 0 01
heart size	0.50	0 79	0 40	0 52	0 30	0 48			
heart volume ml/m² BSA	334 71	62 76	402 22	35 63	4 8 00	47.33	0 01	< 0 001	

not significant

weight values were not statistically significant either before or after surgery

Right ventricular hypertrophy was significantly most marked in the middle group Significant differences were not seen in other respects before or after surgery

Effect of additional factors. On examining separately the 13 girls who in addition to TF had a history of other factors, i.e. prematurity (2 girls) extracardiac congenital anomaly (9), or anomalies in close relations (4 Tables 2 and 3) it is seen that prior to surgery 38 4 per cent were in height and 53.8 per cent in weight below the 2.5th percentile and that after surgery these incidences still were as high as 23 1 per cent and 38 4 per cent, respectively Among the remaining 25 girls in the TF group in whose case such factors were not demonstrable 8 0 per cent were below the 2.5th percentile in height and 12 0 per cent in weight preoperatively and 4.0 per cent and 12 0 per cent postoperatively

Accordingly the presence of one of the above additional factors in girls with TF placed them below the 2.5th percentile more frequently than the girls without such factors.

Comparison between boys and girls (Table 39)

On comparing the groups of boys and girls with TF it was observed that both pre- and post operatively boys were almost significantly more greatly below normal in mean height than girls were and that postoperatively they were almost significantly more greatly retarded in mean weight girls. The mean heart size was enlarged postoperatively almost significantly more in boys than in girls. No significant differences were seen pre- or postoperatively in the other results for boys and girls.

Correlations between the various factors (Table 40)

The correlations between the various factors studied appear from the table on correlation coefficients (Table 40) Postoperatively there was an almost significant correlation between predisposition to infectious diseases and retardation of weight growth The other factors were not found to be correlated to height or weight before or after surgery

Concerning the correlations between other factors may be mentioned that preoperatively the intensity of the systolic murmur had a highly significant inverse correlation with the Hb and Hct levels, i.e the higher the Hb and Hct the less intense the murmur while postoperatively the Hct value had a significant inverse correlation with the intensity of the continuous murmur i.e the more intense the murmur the lower the Hct

Summary of results in the tetralogy of Fallot group

This group consists of 100 children with the tetralogy of Fallot on whom a palliative operation was performed. There were 62 boys and 38 girls, the ratio being 1 6 1 with a predominance of boys (Table 1).

Congenital anomalies in close relations were known in the case of 11.3 per cent of the boys and 10.5 per cent of the girls, the total mean incidence being 11 0 per cent (Table 2).

Prematurely born were 11 7 per cent of the boys and 5 7 per cent of the girls, total mean 9.8 per cent (Table 2)

Extracardiac congenital anomalies had been diagnosed in 22.6 per cent of boys and 23 7 per cent of girls, total mean 23 0 per cent (Table 3)

The mean age at the time of diagnosis of the congenital heart disease was 0.6 year in boys and 0.8 year in girls (Table 4).

The boys mean age at operation was 7.2 years and that of girls 7.6 years (Table 7)

Mortality in all cases submitted in this hospital to palliative operation for TF in the period studied was among boys 5.8 per cent and among girls 2.6 per cent (Table 10).

The mean height and mean weight of the patients in this group were greatly below normal both before and after surgery Some acceleration in height and weight growth occurred postope-

Table 39 *Comparison between boys (6_ cases) and girls (38 cases) in the TF group*

	Height		Weight		Physical capacity		Predisp. to infections		Hb		Hct		RVH		Heart size		Heart vol. ml/m2 BSA	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
Boys	[illegible]	1 53	853 44	86 53	2 58	−0 95	0 37	[illegible]	8.3	1 96	58 54	58 78	1 85	1.50	0 23	63	348.39	396 54
Girls	33	963 97	889 5	10 16	63	−0 95	0 37	0 00	18 7	16 08	61.56	51 26	1 79	1 45	0 13	2	3 1 79	377.50
	05	05		<0 05				<0 05	—	—	—	—			—	05	05	—

not significant

Table 40 Correlation coefficients in the TF group (100 patients)

		1	2	3	4	5	6	7 1)	8	9	10 2)	11	12	13	14	15	16	17 3)	18	19	20 4)
Preoperative height	1	999																			
weight	2	790	999																		
physical capacity	3	098	047	999																	
predisposition to infections	4	103	117	108	999																
systolic murmur	5	020	011	003	329	999															
Hb	6	124	169	143	257	367	999														
1) Hct	7	145	187	295	304	568	881	999													
RVH	8	143	026	108	087	051	039	140	999												
heart size	9	126	099	041	148	301	114	163	015	999											
2) volume ml/m2 BSA	10	157	345	021	076	053	075	051	039	632	999										
Postoperative height	11	893	742	060	072	001	119	121	065	133	120	999									
weight	12	727	880	004	070	108	020	005	052	174	.35	763	999								
physical capacity	13	097	008	398	073	015	130	184	151	006	156	137	066	999							
predisposition to infections	14	146	272	080	206	009	023	016	050	172	093	181	.1	135	999						
continuous murmur	15	023	067	069	029	076	011	080	086	.83	365	041	059	0 1	021	999					
Hb	16	066	037	171	060	315	544	287	056	119	169	011	085	177	040	161	999				
3) Hct	17	09	078	253	166	.40	506	.85	051	113	070	04	055	204	001	1.0	909	999			
RVH	18	038	107	064	052	172	090	011	680	132	008	049	003	294	000	088	042	018	999		
heart size	19	008	115	094	022	028	003	025	093	261	312	062	111	071	055	079	0.1	122	016	999	
4) volume ml/m2 BSA	20	154	318	162	078	105	013	031	[illegible]	171	669	166	247	140	107	064	122	133	210	594	979

P	for 100 observations,	for 88	for 84	for 79	and for 73 observations
0.05	197	210	215	221	30
0.01	257	273	280	288	300
0.001	324	345	353	363	377

1) Determined in 84 cases
2) 79
3) 73
4) 88

*) Significant correlations are underlined

ratively Weight was more retarded than height, and boys more retarded than girls at both times of measurement.

The greatest acceleration in the mean height and weight growth after surgery was seen in the group of TF patients who underwent surgery at the earliest age (under 7 years). However when distributed by sex the boys showed acceleration in *height growth most clearly in the middle* group (7 10 years). There was slight acceleration in the mean height growth of boys in all the age groups. Weight growth in boys, however was accelerated in the two youngest age groups, whereas it was slightly retarded from the preoperative value in the oldest group (11 years and over) The mean weight growth in girls was accelerated only in the youngest group and was slightly retarded in the other two age groups.

Postoperatively the mean physical capacity improved markedly in all the age groups, likewise reduction occurred in the mean haemoglobin and haematocrit levels. The mean heart size increased considerably after surgery

Discussion

Being unselected, this group of 100 consecutive patients with the tetralogy of Fallot chanced to be composed of 62 boys and 38 girls, there being accordingly a predominance of boys. Generally the sexes are known to be equally involved (88 96 126) although there are some series with a distinctly higher incidence among males (20 35 ?1)

?Of the 9? patients whose birth weight was ?n 9.8 per cent had been prematurely born. This incidence of prematurity is higher than that in the general population of Finland in the same period (about 5 per cent, 139 140) Studies in the literature also report an above normal incidence among TF patients (88 100, 1?0).

Extracardiac anomalies had been diagnosed in 23 per cent of the group This is slightly more than in other clinical series of TF in which the incidence is about 13–14 per cent (26 157) Autopsy series naturally include a higher incidence of extracardiac anomalies (100)

Only 4 *per cent of the congenital cardiac* defects had been detected at routine medical examination –26 per cent in the series of Kjellberg and co-workers (91) – and 55 per cent on the basis of symptoms, while in the remaining cases the grounds for the diagnosis were not stated in the case reports.

The preoperative mean height and weight of the TF patients were considerably below normal in the present study as also has been observed in most studies in the literature Following palliative surgery there occurred some acceleration in growth, especially in the group operated on at the earliest age but the mean height and weight remained at levels greatly below the normal

It has been observed (106) that retardation in height of girls with TF increases with age, whereas another study (20) has reported some improvement in physical development after the age of 10 years regardless of whether surgery was performed or not. In the present small group of girls with TF the mean height and weight of the oldest group were closer to normal both pre- and postoperatively than those of the two younger groups.

Weight was more greatly retarded than height, as has been observed also in previous studies (37 106 151) and boys more retarded than girls, which also is an earlier observation (106).

In some studies (37 150) the haemoglobin and/or haematocrit levels were found to be inversely correlated with growth This was not observed in the present study

Other factors were not found to have noteworthy inluence on height and weight growth.

Preoperatively the Hb and Hcr values were found to have a highly significant inverse correlation with the intensity of the systolic murmur In other words, the less intense the auscultation finding, the higher the Hb and Hcr levels. Postoperatively the Hcr value was found to have a significant inverse correlation with the intensity of the continuous murmur i.e the more intense the murmur the lower the Hcr

Surgical mortality in all palliative operations for TF in the period studied was 4 6 per cent. Distributed by sex the mean surgical mortality was *higher in boys (5.8 per cent)* than in girls (2 6 per cent).

heights and weights of both boys and girls were statistically significantly below normal also a year after surgery with some variation in the degrees of significance

3 Mean weight values were generally lower than mean height values. An exception was the group of boys with patent ductus arteriosus, their mean height value was lower both pre- and postoperatively than the mean weight value Likewise the postoperative mean height of girls with coarctation of the aorta was lower than their mean weight but both parameters were within normal limits.

4 Boys were in general more retarded in growth than girls. In the coarctation group however girls had slightly lower height and weight values than boys both before and after surgery In the group of patent ductus arteriosus with pulmonary hypertension the girls were more retarded than boys preoperatively but postoperatively they showed greater acceleration of both mean height and mean weight growth and at follow-up examination a year after operation were less retarded in both respects than boys. In the patent ductus arteriosus and Fallot s tetralogy groups the boys were lower in mean height and weight than girls both pre- and postoperatively

5 Distribution of the patients according to age at operation shows, with one exception, the greatest acceleration in height and weight growth after surgery in the group that underwent operation at the earliest age (under 7 years) this refers to both boys and girls. The exception was the boys group with the tetralogy of Fallot their postoperative acceleration in mean height growth being still greater in the middle group (operated on at 7 10 years of age) than in the youngest group. Height and weight growth acceleration in all the diagnostic groups was smallest in the patients who underwent surgery at the oldest age studied (11 years and over) In this age group sometimes the mean height growth (boys and girls with PDA) and still more often the mean weight growth (girls with PDA boys with coarctation, and boys and girls with TF) were slightly decelerated postoperatively as compared with the respective preoperative growth rates

6 Comparison of the groups with the different congenital heart diseases studied shows that the mean height and mean weight of boys before and after surgery were adversely affected in the following increasing order coarctation of the aorta, PDA PDA+PH TF Some of the differences between the groups were significant (Table 41) The adverse effect on the mean height of girls pre- and postoperatively was a follows in increasing order PDA Co TF PDA+PH The influence on the preoperative mean weight had the same order while the postoperative order was the same as in boys. Co PDA, PDA+PH, TF Part of the differences between the groups were significant (Table 42)

7 No factor was found that would have been correlated with height and/or weight growth in all the disease groups. Physical capacity did not show such correlation in any of the groups. Predisposition to infectious diseases correlated significantly with the preoperative retardation of height and weight growth in the coarctation group only and almost significantly with postoperative weight but not height retardation in the TF group Congestive heart failure and cardiomegaly had before surgery a significant correlation with height retardation and a highly significant correlation with weight retardation in the coarctation group. Hypertrophy seen in electrocardiograms was significantly or almost significantly correlated inversely with mean height and/or weight growth in most of the groups (PDA, PDA+PH, Co) especially before surgery

The correlations between the different factors studied are stated for each disease group in the respective sections.

Examination of the surgical mortalities in all operations for the studied congenital heart defects performed in the hospital during the period concerned shows a higher mortality rate among boys than among girls in all the groups (Table 10). A similar observation was made by Krovetz and Warden when studying the sex distribution of the surgical mortality among 515 patients with patent ductus arteriosus, it was twice as high among males as among females (98). On the other hand, Moller (125) found no sex difference in the mortality in shunt operations for cyanotic heart diseases

Since girls generally are less retarded in height and weight than boys – the difference being particularly distinct in cyanotic congenital heart diseases – it probably is true that the female organism is more resistant to noxa of various kinds, as for example hypoxia. Evidence supporting this theory is found for instance in the report on children who survived the atomic bombing in Hiroshima (65) It may also have a bearing on the higher surgical mortality rate among boys in all the groups in the present study and in general on the greater mortality among male infants in all types of congenital heart defect (7)

Table 41. Comparison of mean height and [illegible] eight [illegible] alues of boys in the different diagnostic [illegible] surgery

	1 PDA 27 boys	2 PDA + PH 13 boys	3 Co 78 boys	4 TF 62 boys	p values 1 2	1 3	1-4	2 3	-4	l
Preop height	927.96	901.23	976 06	880 47		<0 05	<0 05	< [illegible]		
Postop.	946 74	9 2.31	991 41	911.58		0 05		<([illegible]		[illegible]
Preop. [illegible] eight	931.81	873.54	974 45	855 44		<0 05	<0 01	<([illegible]		
Postop.	970 81	897 69	989 90	867 90			<0 001	[illegible]		

not significant

Table 42. Comparison of mean height and weight values of girls in the different diagnostic group bef [illegible] surgery

	1 PDA 73 girls	2 PDA+PH 42 girls	3 Co 22 girls	4 TF 38 girls	P values bet 1 2	1 3	1-4	2-3	2 4	[illegible]
Preop height	967 40	876 43	947.50	933 16	<0.001			0 [illegible]		
Postop.	998.71	931 12	980.91	963 97	<0 01					
Preop. weight	947.23	819.29	940.27	889.53	0 001		0 05	0 1		
Postop.	986.15	916.52	986 73	910 16	<0.01		0 001	0 [illegible]		

In the light of the present study patients who undergo operation at the age of 11 years o over show postoperatively clearly the lowest acceler ation in height and weight growth, and in some groups even deceleration. For this reason it seems recommendable that surgery for the congenital heart diseases here studied is performed during the first 10 years of life preferably at preschool age or in appropriate cases, in infancy However, the postoperative observation time in this study was too short to permit an eval [illegible] final situation even as to height and [illegible] Should it be possible to examine the [illegible] of patients at about the age [illegible] knowledge would be obtained [illegible] ultimate growth of patients submitted [illegible] at different ages. Light would [illegible] on the question whether physical [illegible] considered an appropriate measure [illegible] and harmonious individual [illegible]

REFERENCES

1 Abbott M L. *tlas of congenital heart disease.* Amer Heart A s, New York, 1936

Aeth D to, A Andreone A., Cat na, G Borro L. & Umidon M Gli interventi palliativi nella tetrade di Fallot (Tecnica, indicazioni risultati in 786 casi). *Minerv cardioangiol,* 16 772, 1968

3 Adams, F.H Pulmonary hypertension in hildren due to ongenital heart d sease *J Pediat,* 40 42, 1952

4 Adams, F H Lund, G W & Disenhouse R.B Observations on the physique and growth f children w th ongenital heart disease *J Pediat* 44 674 1945

5 Adams, F.H. & Forsyth, W.B. The effect f surgery on th growth of patient with patent duct arteriosus. *J Pediat* 39 330 1951

6 Adams, P J Adams, F.H. Var R L., Damman J I Jr & M ller W H Diagnosis and tre tment of patent duct rteriosus in inf ncy *Pediatrics,* 12 664 1953

7 Allen, C.M Infa t mortality from congenital cardiac malformatio in Cal fo nia 1957 1960 *Amer J Public Health,* 58 1368 1968

8 Anabtawi, I.N Ellison, R.G & Ellison, L.T Nat al history of p lmonary hypertension in surgically treated patent duct rt riosus. *Circulation,* 31 61 1965

9 Anderson, R C Causative fact rs underlying congenital heart malformations Patent duct arteriosu *Pediatrics,* 14 143 1954

10 Ant nov O S I afin, V I A erko N.N Shurgaya, A M & Chernykh, N I The physical development of childr n suffering f om p tent ductus arteriosus *Pediatria,* 47 7 1968

11 Ash, R & Fische D Manifestations and result of treatment f patent ductus arteriosus in infancy and hildhood an analysis of 138 cases. *Pediatrics,* 16 695 1955

1 Backstrom-Jarvinen, L Height and eight of Finnish children and young adults *Ann Paediat Fenn* 10 suppl 23 1964

13 Backst om-Jarv nen, L., Tiisala R Kantero R L & Hallman, N Illnesse among normal F nnish children during the first five years of lif *Ann Paediat Fenn* 12 13 1966

14 Bake C Brock R Campbell M & Suzman, S Morbus oeruleus Study of 50 ses ft Blalock Taussig operation *Brit Heart J* 11 170 1949

15 Bakhtina G G Lensky G B & Prilepk L P The physical development f y ng hildren suffer ng from F llot tetralogy *Kardiologiia,* 9 26 1968

16 Banik, N D D Westland, R. & Falkner F Growth retardation in cyanotic congenital heart disease. *J Indian Med Ass,* 48 282 1967

17 Banik, N.D D., Westland R. & Falkner F Growth pattern in children with congenital heart disease. *Indian J Pediat,* 36 112, 1969

18 Barnes, A.R. & Harrington, S.W The surgical tr atment of pat nt ductus arteriosus. *Mod Conc Cardiov Dis,* 14 , 1945

19 Bauersf ld S R., Adkins, P C. & Kent E.M. Patent ductus arteriosus in infancy *J Thorac Surg,* 33 1 3 1957

0 Bay r L.M & Robinson, S.J Growth hist ry of children with congenital heart defects. *Amer J Dis Child,* 117 564 1969

21 Benn, J The prognosis of patent ductus arteriosus *Brit Heart J* 9 83 1947

22 Berlind S Bojs, G Korsgren, M & Varnauskas, I Severe pulmonary hypertension accompanying patent ductu arteriosus. *Amer Heart J* 73 460 1967

3 Bing, R.J Vandam, L.D & Gray F D Physiological studies in congenital heart disease Results of preoperatn studies in patient th tetralogy of Fallot *Bull Johns Hopk Hosp* 80 121 1947

24 Bir ks, W Chirurgische Gesichtspunkte der pulmonalen Hypertension *Thoraxchirurgie,* 14 521 1966

25 Blalock A. & Taussig, H B The surgical treatment f malform tion f the heart in which there is p lmonary stenosis or p lmonary tresia *J AMA* 128 189 1945

6 Boesen, I Melchior J C Terslev E & Vendel, S Extracardiac congenital malformations in child ren th congenital heart disease *A ta Paediat Scand* suppl 146 28 1963

27 Bonnet L.M Sur la lesion dite stenose congenitale de l' aort dans la region d l' isthme *Rev Med* (P ris) 23 108 255 335 418, 481 1903

28 Brock, R C Pulmonary valvulotomy f the relief f cong nital pulmonary stenosis. Report f three cases. *Brit Med J* 1 1121 1948.

29 Brom A G Narrowing f the aortic isthmus and largeme t of the mind *J Thorac Cardiovasc Surg* 50 166 1965

30 B rchell, H.B Variation in the clinical and pathologic picture of patent ductus arteriosus. *Med Clin N Amer* 32 911 1948

31 B rf rd T H Ferguson, T.B Goldring, D. & Behrer M R. Coarctatio f the aorta in infants. A linical and xperimental study *J Thorac Surg,* 39 47 1960

32. Burch, G.E. & De Pasquale, N.P. *Electrocardiography in the diagnosis of congenital heart disease* Lea & Febiger Philadelphia, Pa, 1967
33. Burwell, C.S. Patent ductus arteriosus and vascular [illegible]. *JAMA* 154 136 1954
34. Campbell, M. Late [illegible]esults of ope[illegible]tions for Fallot' tetralogy *Brit M J* 2 1175 1958
35. Campbell, M The incidence and later distribution of malformations of the heart. *In* H Watson (ed.): *Paediatric cardiology* Lloyd Luke London 1968, p. 71
36. Campbell, M. & Baylis, J.H. The [illegible]ourse and prognosis of coarctation of the aorta. *Brit Heart J* 18 475 1956.
37. Campbell, M. & Reynolds, G The physical and mental development of children with [illegible]ongenital heart disease. *Arch Dis Child*, 24 294 1949
38. Carlgren, L.E. & Eck, S *In* E. Mannheimer (ed.): *Morbus caeruleus*, S Karger Basel 1947 p. 66.
39. Clatworthy H.W J & McDonald V G J Optimum age for surgical closure [illegible]f patent d[illegible]ct arteriosus *JAMA*, 167 444 1958
40. Cone, T.E., A survey [illegible]f growth [illegible] *Clin Proc Child Hosp* [illegible] 15 [illegible]77 [illegible] 97-98, 1959
41. [illegible]

54. Ellis, F.H. Jr Kirklin, J.W Callahan, J.A & Wood E.H Patent ductus arteriosus [illegible] monary hypert[illegible]nsion. *J Thorac Surg*. 31 [illegible]
55. Engle, M.A. & Goldberg, H.P Coar[illegible]tation [illegible] aorta in children. *Amer J Dis Child*, 9 [illegible]
56. Engle M.A Holswade G R Goldberg, H.P & Glenn, [illegible] Pr[illegible]sent problems pertaining to [illegible] [illegible]f duct[illegible] arteriosus. Persistence of growth [illegible] d[illegible]tion after suc[illegible]essful surgery *Pediatrics* [illegible] 1958
57. Eppinger E.C Burwell, C.S. & Gross, R.E The effect of patent ductus arte[illegible] on the circu[illegible]lation *J Clin Invest* [illegible]0 127 1941
58. E[illegible] R.H Stickler G.B & Weidman, W.H Gro[illegible]th [illegible]f child[illegible]en with congenital heart disease. *Amer J Dis Child*, 117 573 1969
59. [illegible] Engle M.A & Goldberg, H.P. C[illegible]ar[illegible]tation [illegible]f aorta in infancy Analysis of 10 y[illegible] patients with medical management *Pediatrics*, 27 427 1961
60. Cammelgaard A Solem, G Therkelsen, F & [illegible] Late [illegible]esults of operation for patent duct[illegible] arterio[illegible] in infants, especially those [illegible] pulmonary hypertension. *J Cardiovasc Surg*, 6 54 1965

namics tudied before, during and after surgical treatment. *Surg Gynec Obstet*, 92.75 1951

76. Hara, M Dungan, W T Lincoln, B.M & Mc Artcheon, F.B., Patent ductus arteriosus in early infancy *Surgery* 51.396 1962.

77 Hay J.D & Ward, O C. Patent ductus arteriosus. A review of 108 cases treated surgically *Arch Dis Child*, 31.279 1956

78 Holman, E., Gerbode F & Purdy A The patent ductus arteriosus. A review of seventy-fi cases w th surgical treatment including an aneurysm of the ductus of the pulmonary artery *J Thorac Surg*, 25 111 1953.

79 Hubbard, J.P., Emerson, P V & Green, H. Indications for the surgical ligation of a patent ductus arteriosus. *New Engl J Med*, 21.481 1939

80 Hultgren, H Selzer A., Purdy A Holman, E. & Gerbode F The syndrome of patent ductus arteriosus with pulmonary hypertension. *Circulation*, 8 15 1953

81 Joly J-B Kachaner J Huault, G., Gautier M Saint Martin, J Binet, J-P & Langlois, J Une cause meconnue d'insuffisanc cardique aigue mortelle du nouveau-né La persistance du canal artérial. *Arch Franc Pediat*, 25 1105 1968

82 Jones, J C., Complications of the surgery of patent ductus arteriosus. *J Thorac Surg*, 16.305 1947

83 Jones, J C The surgery of patent ductus arteriosus. *Ann Surg*, 130 174 1949

84 Jones, J.C. Twenty-five years experience with the surgery of patent ductus arteriosus. *J Thorac Cardiovasc Surg*, 50 149 1965

85 Jones, J C Dofley F.S. & Bullock L T The diagnosis and surgical therapy of patent ductus arteriosus. *J Thorac Surg*, 9 413 1949

86. Jonsell, S A method for the determination f the heart size by teleroentgenography (a heart volume index). *Acta Radiol*, Stockholm 20.325 1939

87 Kattus, A.A. & Muller W.H., Jr Patent ductus arteriosus with reversal of blood flow Report of a successful surgical closure and physiologic studies. *Ann Surg*, 138:870 1953.

88 Keith, J D Rowe, R D & Vlad, P *Heart disease in children and childhood*. Macmillan New York, 2nd ed. 1967

89 Keys, A & Shapiro, M J Patency of the ductus arteriosus in adults *Amer Heart J* 25 158, 1943

90 Kjellberg, S.R., Lind, J Lönroth, H & Rudhe, U Variations in heart volume in normal children of school age *Acta Radiol*, 41 441 1954

91 Kjellberg, S.R Mannheimer E., Rudhe, U & Jonsson, B *Diagnosis of congenital heart disease*. Year Book Publishers, Chicago 1959

92 Klemetti, A., and Saxén, L The Finnish register of congenital malformations, *Health Services Research of the National Board of Health in Finland*, Helsink 1970.

93 Klepzig, H & Frisch, P *Röntgenologische Herzvolumenbestimmung in Klinik und Praxis*. Georg Thieme Verlag, Stuttgart, 1965

94 Kimner W Probleme der Korrektur von angeborenen Herzfehlern mit pulmonaler Hypertonie *Thoraxchirurgie* 14.530 1966

95 Krovetz L J Weight gain in children with patent ductus art riosus. *Dis Chest* 44 274 1963

96 Krovetz, L.J., Gessner I.H. & Schiebler, G.L. *Handbook of pediatric cardiology*. Hoeber Medical Division, 1969

97 Krovetz, L.J Lester R.G. & Warden, H E., The diagnosis of patent ductus arteriosus in infancy *Dis Chest*, 42.241 1962.

98 Krovetz, L.J & Warden, H E. Patent ductus arteriosus. An analysis of 515 surgically proved cases. *Dis Chest*, 42 46, 1962.

99 Landtman, B. Congenital heart disease in children. *Ann Med Intern Fenn*, 36:542, 1947

100 Landtman, B., Clinical and morphological studies in congenital heart disease. A review of 777 cases, *Acta Paediat Scand*, suppl. 213, 1971

101 Landtman, B. & Hjelt L. Congenital heart disease. A clinical and post mortem study of 246 cases. *Ann Paediat Fenn*, 5 159 1959

102. Lequime, J & Charlier R., Clinique et physiopathologie des cardiopathies congenitales opérables. *Acta Chir Belg*, suppl. 1 1951

103 Levine S.A., The diagnosis of patent ductus arteriosus and the indications for operation. *Acta Med Scand*, suppl. 196, 1947

104 Levine S.A. & Harvey W P *Clinical auscultation of the heart*. Saunders, Philadelphia, 1953 p. 145 147

105 Lind J Heart olum in normal infants. *Acta Radiol*, suppl. 82, 1950.

106 Linde, L.M Dunn, O.J Schireson, R. & Rasof, B., Growth in children with congenital heart disease. *J Pediat* 70 413 1967

107 Little J.A & Sunico, R. Symptomatic patent ductus arteriosus in infancy *J Pediat*, 52 199 1958

108 Lund, G.W Growth study f children with the tetralogy of Fallot. *J Pediat*, 41:572, 1952.

109 Lynxwiler C.P & Wells, C.R.E., Patent ductus arteriosus. A report of 180 operations. *Sth Med J* 43.61 1950.

110 Lyon, R.A. & Kaplan, S. Patent ductus arteriosus in infancy *Pediatrics*, 13.357 1954.

111 Mannheimer E. Patent ductu arteriosus. Diagnosis and indications for operation. *Acta Paediat Scand*, 32 634 1945

112 Mannheimer E. Experiences from operated cases of patent ductus arteriosus. *Acta Paediat Scand*, 35 217 1947

113 Mannheimer E. *Morbus caeruleus*. Karger, Basel, 1949

114 Mannheimer E., Ladtman, B & Hadq ist, T Postoperative course in morbus caeruleus. *Acta Paediat Scand*, 41:518 1952.

115 Mathey J., Binet, J-P Galey J J Dubost, Y & Hazan, E. Resultats du traitement chirurgical de la persistance du canal arterial chez le nourrison. *Arch Mal Coeur* 59 1886 1966.

116. Maxwell, G.M Wurfel, L. & Burnell, R.H. A study of growth in congenital heart disease with a note on the effect of surgery *Austr Ped J* 2 188 1966

117 Mazur J.H Growth failure associated with congenital heart disease. *Clin Proc Child Hosp* (Wash.), 15.87 1959

118 Mc Donald, A.D Congenital defects associated with prematurity *Arch Dis Child*, 37.277 1962.

119 Ke[illegible], T. Mac Mahon, B. & Parsons, C.G., The familial incidence of congenital malformation of the heart. *Brit Heart J* 15:273 1953
120 Mehrizi, A. & Drash, A., Birth weight of infants with cyanotic and acyanotic congenital malformations of the heart. *J Pediat*, 59:715 1961
121 Mehrizi, A. & Drash, A., Growth disturbance in congenital heart disease. *J Pediat* 61:418 1962
122 Mortensen, J.D., Cutler, P.R., Rumel, W.R. & Veasy, L.G., Management of coarctation of the aorta in infancy. *J Thorac Surg*, 37:502, 1959
123 Mustard, W.T., Rowe, R.D., Keith, J.D. & Sirek, A., Coarctation of the aorta with special reference to the first year of life, *Ann Surg*, 141:429 1955
124 Myers, G.S., Scannell, J.G., Wyman, S.M., Dimond, E.G. & Hurst, J.W., Atypical patent ductus arteriosus with absence of the usual aortic-pulmonary pressure gradient and of the characteristic murmur. *Amer Heart J* 41:819 1951
125 Møller, T., Shunt operations in morbus caeruleus. *Acta Paediat Scand*, suppl. 134 1962
126 Nadas, A.S., *Pediatric cardiology*. Saunders, Philadelphia and London, 1963
127 Newman, M., Coarctation of the aorta. Review of twenty-three service cases. *Brit Heart J* 10 [illegible] 1948
128. Nouaille, J., Mathey, J., Schweisguth, O., Labesse, J. & Binet, J.P., La coarctation [illegible] nourrisson, sa correction chirurgicale. *[illegible] Paris*, 41:2610, 1954
129 Nouaille, J., Thibert, M., Gautier, M., [illegible], Mercier, J.N. & Jeune, M., Indications [illegible] de la chirurgie du canal arteriel du [illegible]. *Arch Mal Coeur* 59:1099 1966
130. Okada, R., Johnson, D. & Lev, M., [illegible] malformations associated with [illegible] disease. *Arch Path*, 85:649 1968
131. Overbeck, W., Zum Verschluss des [illegible] bei gleichzeitiger pulmonaler Hypertension. *Thor [illegible] chirurgie*, 14:534 1966
132. Parker, R.L., Pulmonary [illegible] Fallot. *Med Clin N Amer* 32:[illegible] 5 1 48
133 Paul, M.H., Miller, R.A. & Pot[illegible], W.J., [illegible] results of aortic-pulmonary anastomosis for [illegible] tralogy of Fallot. An analysis of [illegible] cases eleven to thirteen years after operation. *Circulation*, 23:525 1961
134 Pelletier, C., Davignon, A., [illegible] P., Coarctation of the aorta in infancy. *Postoperative follow-up*. *J Thorac Cardiovasc Surg*, 7 371 1969
135 Polani, P.E. & Campbell, M., An aetiological study of congenital heart disease. *Ann Hum Genet* 19:209 1955
136 Porter, W.B., The effect of patent ductus arteriosus on body growth. *Amer J Med Sci*, 213 178 1947
137 Potts, W.J., Gibson, S., Smith, S. & Riker, W.L., Diagnosis and surgical treatment of patent ductus arteriosus. *Arch Surg*, 58:612 1949
138 Quetelet, A., Anthropométrie ou mesure des différentes facultés de l'homme. *Anthropométrie* Bruxelles, [illegible] 1
139 Rama, C.L., Prevention of prematurity. *Advances in Pediatr* [illegible] 35 13 1968
140 Rasha, C.I., [illegible] [illegible] [illegible] (Prevention of [illegible] [illegible]). *Duodecim*, 87:801 1971
141 Rathi, [illegible] & Keith, J.D., [illegible] [illegible] blood pressure in [illegible] of the aorta. *Brit Heart J* 26:[illegible] 1964
142 R[illegible], J.M., [illegible], [illegible], [illegible] N., Barclay, R.S., Wild, [illegible], [illegible], W.M. & Inall, J.A., M[illegible] pulmonary hypertension [illegible] [illegible] ductus [illegible]. *Brit Heart J*, 24:[illegible] 1962
143 Re[illegible], [illegible], [illegible], S.A. & Gross, R.E., [illegible]. A review of 104 autopsied cases of the [illegible] 2 years of age or [illegible]. *Amer Heart J* 33:146 1947
144 Richard, M.R., [illegible] postoperative growth patterns in [illegible] heart disease as shown by the [illegible]. *J Pediatrics*, 9 77 1952
145 R[illegible], S.J. & [illegible], E.M., Growth history of children with congenital heart defects. Effect of [illegible] [illegible]. *Child Develop*, 40 315 1969
146 R[illegible], A.M., M[illegible], [illegible] A.S. & Gross, R.E., [illegible] [illegible]. A clinical and [illegible] study of 21 patients in the first year of life. *Pediatrics*, 22:[illegible] 1958
147 [illegible] & [illegible] C., Surgical treatment [illegible]. *Acta Chir Scand*, 1[illegible] 1951
148 S[illegible] & [illegible] J., Congenital defects. Holt, Rinehart & Winston, New York 1969 p 3 and 5
149 [illegible] R.I., The first serial study of human [illegible]. *Amer J Phys Anthrop*, 10:329 1927
150 [illegible] A., [illegible] H. & H[illegible] H.H., Zur [illegible] der [illegible] Entwicklung bei angeborenen Herzfehlern. *Arch Kreisl Forsch*, 24 1 1956
151 [illegible] H., Die körperliche und geistige Entwicklung bei Kindern mit angeborenem Herz und [illegible]. *Arch Kinderheilk*, Suppl. 47 1962
152 [illegible] S.R. & [illegible] R.I., Surgery for coarctation of the aorta. A review of 400 cases. *J Thorac Cardiov Surg* 44 54 1962
153 [illegible] I.H., Patent ductus arteriosus. *Brit Heart J* [illegible] 1948
154 [illegible] M.J., The preoperative diagnosis of patent ductus arteriosus. *JAMA* 126:734 1944
155 [illegible] M.J., Recent advances in surgical treatment: A patent ductus arteriosus. *Mod Conc Card [illegible]* 16 1 1947
156 [illegible] M.J. & Kays, A., The prognosis of untreated patent ductus arteriosus and the results of surgical intervention. A clinical series of 50 cases and an analysis of 139 operations. *Amer J Med Sci* 2[illegible] 174 1943
157 [illegible] H.B., [illegible] H. & Mandelbaum, I., Results of shunt procedures in tetralogy of Fallot. *Surgery* 47 [illegible] 1960
158 [illegible] A.W., Kirklin, J.W., [illegible] P.H., [illegible] & Wood, E.H., [illegible] of pulmonary hypertension after closure of patent ductus arteriosus. *Proc Mayo Clin* 29 [illegible] 1954
159 [illegible] H.D. & Humphreys, C.H., The atypical ductus: Physiologic and technical considerations in its surgical therapy. *Surgery* 41:112, 1957

160. Smeloff E.A. Bauersfeld S.R. & Kent, E.M. Coarctation of the aorta in infant and children. *Ann Surg*, 146:450 1957
161. Sulamaa, M., *Personal communication.*
162. Takkunen, R-L., Antropometric studies on Finnish children. *Ann Pediat Fenn*, Suppl. 19 196
163. Taussig, H.B. Diagnosis of tetralogy of Fallot and indications for operation. *J Thorac Surg*, 16:41 1947
164. Taussig H.B., *Congenital malformations of the heart.* Harvard University Press, Cambridge 1960
165. Taussig, H.B. Crawford H. Pelargonio S. & Zacharioudakis, S. Ten to thirteen year follow-up on patients after a Blalock Taussig operation. *Circulation*, 25:630, 196
166. Touroff A.S.W. The indication for operation in patent ductus arteriosus. *N Y St J Med* 49:1722, 1949
167. Trusler G.A., Arayangkoon, P. & Mustard, W.T. Operative closure of isolated patent ductus arteriosus in the first two years of life. *Canad Med Ass J* 99:879 1968.
168. Umansky R. & Hauck A.J. Differential growth among children with patent ductus arteriosus. *Amer J Dis Child*, 102:563 1961
169. Umansky R. & Hauck, A.J., Factors in the growth of children with patent ductus arteriosus. *Pediatrics*, 30:540 1962.
170. Ward O.C & Dowse C. Association of extracardiac anomalies with congenital heart disease. *Irish J Med Sci*, 1 423 1968
171. Wasastjerna, S.O. Trenne fall af öppen ductus Botalli. *Finska Läk Sällsk Handl*, 16:235 1874
172. Waterman, D.H. Samson, P.C. & Bailey C.P. Surgery of patent ductus arteriosus. *Dis Chest*, 9:102, 1956.
173. Wiland O.K. Extracardiac anomalies in association with congenital heart disease. *Lab Invest*, 5:380, 1956
174. Yu, P.N. Lovejoy F.W. Jr & Joos H.A. Nye, R. E. Jr & Beatty D.C., Studies of pulmonary hypertension. *Amer Heart J* 48:544 1954
175. Ziegler R.F. *Electrocardiographic studies in normal infants and children.* Thomas, Springfield, Ill, 1951
176. Ziegler R.F. The importance of patent ductus arteriosus in infants. *Amer Heart J* 43:553 1952.